HUMAN SUBJECTS RESEARCH
AT
LAWRENCE LIVERMORE NATIONAL LABORATORY

INFORMATION, POLICIES, AND PROCEDURES FOR THE REVIEW AND ETHICAL CONDUCT OF HUMAN SUBJECTS RESEARCH

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1.0 Introduction

Directorates across Lawrence Livermore National Laboratory (LLNL) are working on research projects to further our knowledge of human biology and disease. The use of human subjects in these research activities falls under the jurisdiction of federal regulations. LLNL investigators are granted the privilege of involving human subjects in their research under the terms of a formal assurance with the Office for Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS). All LLNL employees or contractors who conduct, support, or review research involving human subjects must comply with the regulations identified in this assurance, as well as applicable state and institutional policies and standards of professional conduct and practice. Failure to comply with the terms of the assurance can result in loss of funding for human subjects research. Non-compliance by one investigator can affect the ability of all others at LLNL to do human subjects research.

LLNL's Multiple Project Assurance, #1415-01, maintained with the OHRP at DHHS, requires that all human subjects research conducted by LLNL employees or contractors, or otherwise under the auspices of LLNL, be performed in accordance with Title 45 Code of Federal Regulations, Part 46 (45 CFR 46).[1] In addition, the actions of LLNL must also conform to all other applicable federal, state, and local laws and regulations, including FDA, DOE, University of California, and LLNL policies and procedures.

It is also LLNL's policy that investigators respect and protect the rights and welfare of individuals recruited for or participating in research conducted by or under the auspices of the Laboratory. In the review and conduct of research involving human subjects, LLNL is guided by the ethical principles set forth in the Belmont Report (i.e., respect for persons, beneficence, and justice).

As delegated by the Laboratory's Director, LLNL's Institutional Review Board (IRB) has the primary responsibility for the oversight of the protection of human subjects who have been recruited to participate or are actively participating in research projects conducted by or with the assistance of LLNL employees or contractors.

This document provides information about the ethical conduct and review of human subjects research at LLNL. It explains the various federal and state regulations and institutional requirements, and provides guidance for investigators and IRB members regarding the development, review, and conduct of human subjects research.

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1. 45 CFR 46 consists of Sub-parts A, B, C and D. Sub-part A is also known as the "Common Rule". The text of this rule was agreed upon by seventeen government agencies and published in the Federal Register on June 18, 1991. The agencies all agreed to promulgate the same regulations based on this Common Rule so that human subjects research would be regulated consistently across the government. The Federal Register made it clear that each agency would implement the Common Rule through its particular regulations; DOE does so through 10 CFR 745. LLNL's Multiple Project Assurance with DHHS commits the Laboratory to implementing all sub-parts of 45 CFR 46, not just the Common Rule. Therefore, when referencing federal regulations, this manual will use the DHHS regulations (45 CFR 46) instead of DOE regulations (10 CFR 745) when referring to elements of the Common Rule.

The information presented here is the most current available. However, the field of human subject protection continues to evolve. Investigators and Board members are encouraged to check the LLNL IRB Web site, http://www.llnl.gov/HumanSubjects, for revisions or updates.

The IRB Office is also available to answer any questions investigators may have regarding the participation of human subjects in research. To contact the IRB Office please use the following telephone number and address:

IRB Office
7000 East Ave, L-448
Livermore, CA 94550
Phone: 925-422-8069
Fax: 925-422-8226
Email: dake1@llnl.gov
Office location: B3703, R1258

1.1 Research: A Shared Responsibility

The Laboratory, research staff, the IRB Office, and the IRB share collective responsibility for the ethical conduct of human subjects research. To be effective, this collaborative responsibility requires a culture of trust, openness, and honesty. LLNL must uphold the highest ethical principles in the conduct of research. By upholding the highest standards in a safe research environment, LLNL can build public support for the pursuit of greater knowledge.

The dignity and welfare of individuals who participate in research is a central concern in the protection of human subjects. Our primary goal must be to assure the development of a fair and explicit process in which subjects voluntarily decide to participate in a study based on an intelligent and knowledgeable assessment of the risks and benefits of the research.

Review of human subjects research performed by employees, participating guests, students, or contractors of LLNL is required. This review is conducted by the Laboratory's IRB. Composition of the IRB is mandated by the federal regulations, which require scientific and non-scientific individuals from various directorates at LLNL, as well as community representatives who are not affiliated with the Laboratory.

The IRB is charged with a twofold mission to (1) determine and certify that all projects reviewed by the IRB conform to the regulations and policies set forth by the DHHS regarding the health, welfare, safety, rights, and privileges of human subjects and (2) assist investigators in conducting ethical research that complies with the DHHS regulations in a way that permits accomplishment of the research activity.

The mission is accomplished through IRB review of protocols, discussion between investigators and the IRB during the review process, and IRB/IRB Office outreach to the research community. The process serves to ensure the safe and ethical conduct of human research and the protection of the rights and welfare of human subjects.

1.2 The Ethical Foundations of 45 CFR 46—The Belmont Report

The passage of the National Research Act in 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In 1976, the Commission published the Belmont Report, which articulates the basic ethical principles that guide the conduct of research with human subjects and form the foundation for federal regulations governing the protection of human research subjects. In the report, three principles were defined as basic to the protection of human subjects: respect, beneficence, and justice. The LLNL IRB accepts and promulgates these ethical principles.

> ***Respect***—In consideration of respect for persons, investigators are required to seek voluntary, written informed consent from potential subjects. Voluntary informed consent means that subjects are (1) given explicit assurances of the voluntary nature of their participation in terms that are easy to understand and (2) not under duress at the time they are asked to participate in the research. The consent form also includes adequate information about the study to assist subjects in intelligently deciding whether to participate in research. In addition, respect means honoring the privacy of individuals and maintaining the confidentiality of their data. Respect for minors and decision-impaired persons requires extra precautions to protect those individuals who are immature or incapacitated, perhaps even to the extent of excluding them from participation in certain research. The extent of protection depends on the risks and benefits of the research to the participants.
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> ***Beneficence***—This principle requires that investigators maximize the potential benefits to the subjects and minimize the potential for harm. The probability of benefits to the subjects, or in the form of generalized knowledge gained from the research, should always outweigh the probability of harm. Finally, if there is any harm resulting from participation in the research, then there must be an off-setting and compelling benefit, either to the subject or society in general.
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> ***Justice***—The principle of justice requires that subjects be selected fairly and that the risks and benefits of research are distributed equitably. Investigators should take precautions not to select subjects simply because of the subjects' easy availability (e.g., co-workers), their compromised position (e.g., prisoners), or because of social, racial, sexual, economic, or cultural biases institutionalized in society. Investigators should base inclusion criteria on those factors that most effectively and soundly address the research problem, not on the easy availability of certain populations.

1.3 Human Subjects Research Defined

In defining human subjects research activities, two separate determinations must be made. The first determination is whether or not the activity can be considered research. If the answer is "yes," investigators must follow up with a second determination: does the research involve human subjects? This determination must be made following 45 CFR 46's definitions of the terms "research" and "human subjects":

Research—"a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research, whether or not they are conducted or supported under a program which is considered research for other purposes." Investigators unsure of whether an activity constitutes human research should contact the IRB Office. (Appendix 11 provides additional information about research in the occupational/public health environment.)

Human subjects—"living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." Investigators should note that although cadavers are not considered "human subjects", information collected from them can result in an investigator obtaining information about the cadaver's living relatives (e.g., genetic studies). Activities in which a researcher collects private, identifiable information about third parties would meet the definition of "human subjects".

All research involving human subjects must be screened by the Laboratory's IRB Office to determine whether further review and approval by the IRB is required. This review must take place before the research activity is initiated. The requirement applies to all research involving human subjects and all activities that even in part involve such research, if one or more of the following apply:

- The activity is sponsored, in part or entirely, by LLNL.
- Some or all of the activity is conducted by, or under the direction of, any LLNL employee or subcontract worker in connection with his or her Laboratory duties.
- Some or all of the activity is conducted by, or under the direction of, any LLNL employee or subcontract worker using any LLNL property or facility.
- The activity involves the use of LLNL's nonpublic information to identify or contact human research subjects or prospective subjects.

The term "human subjects research" potentially covers a broad range of activities. The following list provides a few examples of research activities that require IRB review and approval:

- The use of human-derived data.
- The use of human cell cultures.
- Projects or pilot studies in which the investigator is the only subject.
- Research projects in which information is sought or obtained either directly from the subject (e.g., through an interview or questionnaire) or indirectly (e.g., through observation of human subjects or access to identifiable private records).
- Collaborative studies in which human material or information is collected at another institution and sent to investigators at the Laboratory.
- Requests for information from third parties interested in conducting human subjects research or concerning existing human subjects research.

- Donation of tissues, organs, fluids, or other bodily material for research purposes.
- Research projects that require human subjects to participate in physical activities.
- Evaluation of medical devices that are being developed to evaluate health or detect disease.
- Research involving experimental or licensed pharmaceuticals.

> ***Note**: When an investigator is unsure whether or not an activity involves human subjects or should be considered research, s/he should contact the IRB Office for an administrative review. The IRB Office will review supporting documentation of the activity and promptly notify the investigator of the results of the review.*

2.0 Information for Investigators

2.1 Introduction

Although the Laboratory, investigators, the IRB, and the IRB Office share collective responsibility for the ethical conduct of human subjects research, the complex responsibilities of doing so can make the investigator's role particularly difficult and challenging. However, once the investigator understands the responsibilities involved, research can be rewarding for both the investigator and the subjects who participate. This chapter discusses the investigators' responsibilities and provides additional information regarding the development of a human subjects research protocol and conducting a successful research study.

2.2 Investigator Responsibilities

Any investigator who conducts research involving human subjects must comply with Federal regulations governing human subjects research, as well as applicable state and institutional policies and standards of professional conduct and practice. Failure to comply with Federal regulations can result in loss of funding to conduct human subjects research by the individual, the program, or the Laboratory. Non-compliance by one investigator can affect the ability of all others at LLNL to do human subjects research. An investigator must:

1. understand the ethical standards and regulatory requirements governing the research activities,
2. recognize that IRB review and approval **must** precede initiation of any work involving human subjects,
3. notify the IRB of their intention to use human subjects in research and submit required material to the IRB to facilitate review of research,
4. protect the rights and welfare of the human subjects who participate in the research through proper informed consent, etc., and
5. notify the IRB of any adverse or unexpected events regarding subjects or changes to the research protocol.

> ***Note**: When an investigator is unsure whether or not an activity involves human subjects or should be considered research, s/he should contact the IRB Office for an administrative review. The IRB Office will review supporting documentation of the activity and promptly notify the investigator of the results of the review.*

All investigators at LLNL who are engaged or plan to be engaged in research involving human subjects must successfully complete the Web-based course, HS0035-W (Human Subjects Research Training), which is available at http://www-training.llnl.gov/wbt/hc/HS0035/HSR01.html. To stay abreast of changes in regulations and procedures, investigators must repeat this course every two years. Additional training is available from the IRB Office staff on an as-needed basis.

The IRB Web site, http://www.llnl.gov/HumanSubjects/, should be consulted for new and revised institutional and federal guidelines, policies and procedures, forms, etc. relating to human subjects research.

2.3 Research Eligible for Administrative (Exempt) Review

Some research involving human subjects, their bodily materials, or personal data does not require IRB review and approval, but does require administrative review by the IRB Office. In order to fulfill federal requirements for the proper review of these activities, LLNL has assured the DHHS that **all** research activities involving human subjects or their identifiable, private information, whether funded or not, will be reviewed by the IRB Office to determine whether or not further review by the IRB is appropriate. If the IRB Office determines that the research is exempt from federal requirements governing human subjects research, the Office will issue a Notice of Exemption. If the activity does not qualify for a Notice of Exemption, the investigator is notified by the IRB Office within three working days of submitting the request and subsequent review and approval by the IRB will be required.

2.3.1 Research Exempt from 45 CFR 46

45 CFR 46 identifies several categories of human subjects research activities that may not require review by the IRB. These exempt categories do not apply to research involving (1) deception of subjects where the investigator does not disclose the true purpose of the research and/or the results of the subject's participation in the study; (2) sensitive behavioral research, or (3) research involving pregnant women, in vitro fertilization, prisoners, the mentally disabled, or other "vulnerable" populations. The exemption categories follow.

2.3.1.1 Existing Data, Documents, Records, or Specimens

Research in which the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens is considered "existing" if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects. Note: Research involving human ova (fertilized or not) is not exempt. (Please see Section 2.3.2 "Additional Considerations" for further clarification regarding anonymous or existing data, documents, etc.)

2.3.1.2 Tests, Surveys, Interviews, or Observation of Public Behavior

There are three types of research that fall into this category:

- Research involving the use of educational tests (e.g., cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or observation of public behavior, **unless**: (1) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects; and (2) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. The IRB Office is required to review copies of the informed consent form and proposed questionnaires or survey instrument(s) prior to approval and implementation. Survey or interview procedures involving children do not qualify for this exemption. (Please see Section 2.3.2 "Additional Considerations" for further information about research involving surveys or questionnaires.)
- Research involving the use of educational tests (e.g., cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or observation of public behavior that is not exempt under Section 2.3.2.2 "Existing Data" if (1) the human subjects are elected or appointed public officials or candidates for public office or (2) federal statute(s) require(s), without exception, that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. (Please see Section 2.3.2 "Additional Considerations" for further information about research involving surveys or questionnaires.)
- Research conducted in established or commonly accepted educational settings that involve normal educational practices, such as (1) research on regular and special education instructional strategies or (2) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2.3.1.3 Public Service or Benefit Programs

This category includes research and demonstration projects that are conducted by or are subject to the approval of department or agency heads, and that are designed to study, evaluate, or otherwise examine (1) public benefit or service programs, (2) procedures for obtaining benefits or services under those programs, (3) possible changes in or alternatives to those programs or procedures, or (4) possible changes in methods or levels of payment for benefits or services under those programs.

2.3.1.4 Taste and Food Quality Evaluations at the DHHS

This category includes taste and food quality evaluation and consumer acceptance studies if (1) wholesome foods without additives are consumed or (2) a food is consumed that contains either (a) a food ingredient at or below the level and for a use found to be safe or (b) an agricultural chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration (FDA) or one approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA).

2.3.1.5 Fee-for-Service Activities Performed in Support of Research

Based on federal guidance from the OHRP, the LLNL IRB has determined that LLNL employees are considered not to be "engaged" in human subjects research if:

1. their involvement is limited to performing commercial services for outside organizations or institutions (or performing other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), and
2. they adhere to commonly recognized professional standards for maintaining privacy and confidentiality (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis).

Fee-for-service activities are not reviewed by the convened IRB. However, the IRB Office does review the requests to verify that the human subjects research activity has received appropriate IRB review and approval at the initiating institution(s). Accordingly, the IRB Office will require the following information from the Chair of the reviewing IRB:

- Title of study.
- Date of the latest IRB approval.
- Information regarding vulnerable populations (i.e., pregnant women, fetuses, children, prisoners, or the decision-impaired). Specifically, if the study involves vulnerable populations. If so, the vulnerable population should be identified.
- Acknowledgement that samples will be analyzed at LLNL as a fee-for-service activity.
- Review of IRB's Multiple Project or Federal-wide assurance number.

Investigators should note that due to ethical and legal concerns regarding human subjects research in foreign countries, the LLNL IRB does not currently allow fee-for-service determinations if human subjects are recruited or if samples or subject data are obtained from outside the United States.

If an investigator believes that s/he may be involved in a fee-for-service activity, the investigator must complete Form HSR-7, "Request for Fee-for-Service Determination", and return it, along with supporting documentation, to the IRB Office at L-448. The IRB Office will respond to requests for fee-for-service determinations within 3-5 business days.

2.3.2 Additional Considerations

Although research in the above mentioned categories may not require review by the IRB, there are additional concerns that the IRB Office will consider during the administrative review, and which may impact on the final determination. Receiving a Notice of Exemption does not mean that the investigator is exempted from addressing these concerns.

2.3.2.1 Anonymous Data

Data are considered to be anonymous when there is no possible way to identify the participants from the data collected. Data are not anonymous if anyone, or any procedure such as accessing a computer database, will identify the subject. In most instances, the omission of specific identifiers, such as name, social security number, or patient number, is sufficient to qualify a study as anonymous. Sometimes an investigator may preserve a subject's anonymity while still retaining data on individual characteristics such as age, gender, ethnic origin, occupation, or diagnosis. Anonymity is possible only when studying large samples or populations. When the number of potential participants is small and/or the research setting is identified, anonymity can be threatened or compromised even when identifiers have been removed from the data.

Archived pathology or diagnostic specimens that are considered residual biological material and destined to be destroyed can be used in research. They are considered exempt from IRB review if there are **no** patient identifiers linked to the specimen and if the data is not intended to be used in the diagnosis or treatment of a patient. If either of these conditions apply, then consent of the research subject is required and the study will require IRB review.

Use or collection of anonymous human biological specimens for research efforts focused on understanding, diagnosing, and treating genetic diseases will require review by the IRB. There are additional ethical concerns for genetic research (e.g., the potential for discrimination with regards to employment or insurability) that may not apply for other types of research with biological specimens. Please contact the IRB Office for additional information.

2.3.2.2 Existing Data

The term "existing" refers to the time period that the data or material was obtained. Federal guidance clearly states that the term "existing" refers to material or tissue that was "archived" or "on the shelf" prior to IRB review of the research. If the data/specimens are collected after the submission of the IRB application, then the data are not pre-existing or "archived", the protocol will require IRB review, and the investigator may be required to obtain written informed consent.

Specimens received as extra material or extra specimens requested from a physician conducting a clinical procedure are not pre-existing or "archived" and thus require written informed consent from the subject and review by the IRB. If there is a link to the patient's identity and a possibility that the patient may be contacted in the future, an informed consent document is required. Furthermore, informed consent is required if there is a link to the patient's identity and a possibility that the research may result in commercial or economic value.

Use of existing human biological specimens for genetic research will require review by the IRB. There are additional ethical concerns for genetic research that may not apply for other types of research with biological specimens. Please contact the IRB Office for additional information.

2.3.2.3 Research Involving Surveys or Questionnaires

2.3.2.3.1 Sensitive survey research

Sensitive surveys or questionnaires are seldom exempt from IRB review. A sensitive survey includes questions about illegal activities or highly personal aspects of the subjects' behavior, life experiences, or attitudes. Examples include chemical substance abuse, sexual activity or attitudes, sexual abuse, criminal behavior, sensitive demographic data, detailed health history, etc. The potential for provoking a negative emotional reaction from subjects, their families, or the community is a principal determining factor of sensitive survey research.

2.3.2.3.2 Breaches of confidentiality

Additional consideration for exemption includes determining if there is a risk associated with a possible breach of confidentiality (i.e., accidental disclosure of drug use to law enforcement personnel). In surveys with potential psychological risk, review for exemption includes risks associated with surveys about sensitive topics as well as those resulting from a breach of confidentiality. When confidentiality is an issue, the presence or absence of subject identifiers may be a decisive factor.

2.3.2.4 Use of Consent Forms

A Notice of Exemption does not necessarily exempt investigators from the requirement of obtaining written informed consent from subjects. Most research involving surveys, questionnaires, or otherwise interacting with subjects will require the use of a consent form. For studies where there are no subject identifiers (i.e., when anonymous data is collected), an information sheet or cover sheet is usually required. Additional information regarding consent forms is available in Section 2.8 "The Consent Process".

2.3.3 Submitting a Request for Administrative Review (HSR-4)

> ***Note**: Investigators are strongly urged to consult with the IRB Office before submitting activities for administrative review.*

If an investigator believes his/her research qualifies for an administrative review, the investigator must submit Form HSR-4, "Request for Administrative Review" to the IRB Office, along with the following documents, as applicable:

- A brief abstract of the research activity that includes the purpose and objectives of the study.
- Approval from other participating institutions.
- Recruitment materials (i.e., advertisements, flyers, phone scripts, etc.).
- A sample consent form or information sheet.

- Copies of surveys, educational tests, or interview scripts.

When submitting a fee-for-service activity to the IRB Office for an administrative review, the investigator must submit Form HSR-7, "Request for Fee-for-Service Determination". Please review Section 2.3.1.5 "Fee-for-Service Activities Performed in Support of Research" for additional information.

2.4 Research Requiring IRB Review

2.4.1 General Requirements

Any research activity that does not qualify for an administrative review must be reviewed by the IRB to determine if the rights and welfare of human subjects involved in the research activity are adequately protected. Documents provided to the IRB by investigators must contain enough information to allow valid judgments about the science and ethics of the research. After a protocol has been approved, an investigator must submit an application renewal request to the IRB. The investigator must also receive approval from the IRB before any changes to the research protocol are implemented or if any subject experiences an adverse event as a result of participating in the research activity.

2.4.2 Pilot Studies

Pilot studies and feasibility studies, even if they include only one subject, require the same consideration by the IRB as a project that requests the participation of 100 or more subjects. Investigators interested in conducting feasibility or pilot work should consider contacting the IRB Office prior to submitting an application. The IRB Office can advise the investigator on how to appropriately address issues related to the risks and benefits of participation.

2.4.3 Research Collaborations with Off-Site Institutions or Investigators

Human subjects research that involves off-site collaborations must be reviewed by the LLNL IRB as well as the collaborating institution's IRB. This is true regardless of whether the LLNL investigator has contact with the subject or not. Additionally, IRB review is required even if LLNL investigators only have access to coded information or samples. When research involves off-site institutions, it is important that all collaborators work closely together to develop a protocol and consent form that will be acceptable to all reviewing IRB offices.

> ***Note**: Do not wait for the IRB approval at collaborating institution's before submitting your proposal to the IRB. If all human subject contact occurs at the collaborating institution, and the LLNL IRB approves the project prior to your obtaining an approval letter from the collaborating institution's IRB, the LLNL IRB will simply note that your project's approval is contingent upon the receipt of your collaborator's IRB approval.*

2.5 The Basic Application Packet

Most IRB applications for human subjects involved in biomedical research consist of four core documents: (1) Form HSR-1, "Request for Review", (2) Form HSR-2, "Application to Involve Human Subjects in Research", (3) Consent Form, and (4) Bill of Rights. These forms are available at http://www.llnl.gov/HumanSubjects/forms.html or from the IRB Office. Other documents may be required as part of the submission depending on the type of research (e.g., collaborations, FDA-regulated studies, etc.).

All investigators should carefully review the following requirements for submission of applications to the IRB. Submission of incomplete application packets **will** result in the delay of the review and approval process. The review process will not be initiated if the proposal is incomplete and/or does not fulfill the IRB's requirements described in Section 2.6, "Guidelines for Developing a Basic Protocol". Investigators should also pay close attention to information provided in Section 3.4, "IRB Review Process", and the guidelines provided on Form HSR-2, "Application to Involve Human Subjects in Research", in order to ensure that the appropriate forms are submitted for IRB consideration.

The IRB Office is always available to answer any questions investigators may have regarding the participation of human subjects in research or the review of applications by the IRB. To contact the IRB Office please use the following information:

IRB Office
7000 East Ave, L-448
Livermore, CA 94550
Phone: 925-422-8069
Fax: 925-422-8226
Email: dake1@llnl.gov
Office location: B3703, R1258

2.5.1 Request for Review (Form HSR-1)

Form HSR-1, "Request for Review", is a cover sheet that provides the IRB with basic information about the principal investigator and the proposal. The information provided on this form will facilitate an effective review by all members of the IRB.

2.5.2 Application to Involve Human Subjects in Research (Form HSR-2)

Form HSR-2, "Application to Involve Human Subjects in Research", is an official account of the intended research methods and procedures, with special attention paid to how benefit is maximized and risk minimized and autonomy respected. This protocol application clarifies what is to be done, how, and why. Additional guidance regarding the development of a protocol can be found in Section 2.6, "Guidelines for Developing a Basic Protocol".

LLNL is legally responsible for research conducted at LLNL, sponsored by LLNL, or using LLNL's non-public information—as are investigators and their supervisors. Therefore, IRB protocols must reflect what is actually done in the research. Once the IRB has approved a protocol for a particular project, the investigator is bound to follow that procedure. If the investigator decides to change the protocol, s/he must receive approval from the IRB prior to initiating the change.

The protocol is a control document—an official statement that specifies how the study is being conducted. It is a document that all researchers associated with the project are expected to read and follow. The protocol becomes a vital part of an official "paper trail" showing that the research is acceptable to a legally constituted board of reviewers. Should anyone raise questions about the research, the approved protocol is powerful evidence that the project is of sufficient value to justify any risks or inconveniences involved.

2.5.3 Consent Form

When subject contact occurs at LLNL, the LLNL investigator must create and submit a consent form to the LLNL IRB for review and approval. A sample Consent Form is available at http://www.llnl.gov/HumanSubjects/forms.html. Once approved, the Consent Form will be stamped with an effective date and expiration date. All subjects participating in the research must read, sign, and be given a signed copy of the approved consent form prior to participating in the research activity. Please refer to Section 2.8, "The Consent Process," for additional information regarding the requirements for informed consent.

If the protocol involves a collaboration with another institution and subject contact occurs at that institution, the LLNL IRB may accept the collaborating institution's Consent Form in lieu of an LLNL Consent Form. Acceptance by the LLNL IRB depends on whether or not the collaborating institution's Consent Form contains the elements of consent as described in Section 2.8, "The Consent Process".

2.5.4 Experimental Subject's Bill of Rights

The State of California requires that all subjects enrolled in biomedical research receive a copy of the Experimental Subject's Bill of Rights. LLNL investigators are responsible for ensuring that subjects recruited for medical research at LLNL are provided with a copy of the "Bill of Rights" (available at http://www.llnl.gov/HumanSubjects/forms.html) in addition to the IRB-approved Consent Form.

2.6 Guidelines for Developing a Basic Protocol

A research protocol is intrinsic to planning ethically responsible research and to working with the LLNL IRB. In developing a human subjects research protocol, investigators should contemplate systematically (in writing) the research rationale, methods, and procedures, and the steps that will be taken in response to ethical considerations. The LLNL IRB encourages investigators to view the protocol as a planning tool, not simply a bureaucratic hurdle; it is not a form to be tossed together at the last minute. Investigators are encouraged to think through the ethical considerations along with the methodological ones. Treating ethical considerations as an afterthought in the protocol development process can unfortunately lead to a research plan that is not workable or approvable from the IRB's perspective. Keeping that in mind, investigators are encouraged to consider the following guidelines when developing a protocol.

2.6.1 Abstract of the Project

DOE requires that LLNL annually provide them with an abstract for each human subjects research project requiring IRB review. In order to meet DOE requirements, the abstract should provide a summary of the proposed project and consist of no more than 750 words. It should be written in non-technical language and should clearly explain the LLNL investigator's role in the research activity. The abstract will be forwarded to the U.S. Department of Energy (DOE) to satisfy LLNL's annual reporting requirements. The DOE will post the abstract on a public server. Therefore, it should not contain sensitive information.

2.6.2 Detailed Description of the Protocol

A detailed description of the protocol will include a discussion of the following eight topics.

2.6.2.1 Purpose, Methods, and Procedures

The purposes, methods, and procedures section of the protocol should include the following elements:

- The title and sponsor of the study.
- The purpose of the research and the hypotheses to be tested.
- The historical background of the research, referencing key scientific literature to a maximum of 10 articles.
- An account of the research method, design, and mode of analysis, detailed enough that reviewers can assess scientific validity, including a fully detailed account of procedures that directly affect subjects, their bodily materials, or data.

- The location of the research—specify the exact laboratory, community, institution, etc., where various components of the research are to be performed, the reason why that setting was chosen, and how the investigator happens to have access to it.
- The duration of the project and how this window of time coincides with other time constraints, such as the duration of funding, etc.

2.6.2.2 Subject Selection Process

The research protocol should indicate how many subjects will be included in the study and, where relevant, the ethnic background, sex, age, and state of health of prospective subjects. It should explain why a particular population is being used, the source(s) from which subjects will be recruited, and a statement of the selection criteria.

In addition to the above information, investigators will also need to give careful thought and attention to their recruitment procedures. That information must also be presented to the IRB and detailed in the research protocol.

Further information and guidelines regarding recruitment and selection of subjects is discussed below.

2.6.2.2.1 Recruitment of subjects

Respect for potential subjects begins with recruitment procedures that ensure the voluntary participation of the subject. Recruitment is the dialogue that takes place between an investigator and a potential subject prior to the initiation of the consent process. In many cases, it is the introduction to the consent process.

Various recruitment tools can be used to inform potential subjects of a research activity and provide them with an opportunity to contact the investigator. Recruitment tools may include post-cards, flyers, advertisements, press releases, brochures, verbal exchanges, and postings on the internet. The IRB must review and approve any recruitment tool. Copies of all recruitment materials should be included with the initial application. If the material is not ready at the time of initial application, investigators may submit the material as an amendment to an already approved project. In all cases, recruitment tools must be approved prior to their use. Advertisements, press releases, etc., may qualify for expedited review. The content of advertisements should be limited to the following information:

- The name of the investigator and contact information.
- A simple and concise description of the purpose of the research.
- General eligibility criteria for participation.
- A truthful description of the possible benefits which may result from participation in the research. If there are no benefits, please indicate whether subjects are paid for their participation or receive free treatment.

2.6.2.2.2 Selection of subjects

The systematic selection of subjects based on easy availability, their subordinate position, or social, racial, sexual, economic, or cultural biases institutionalized in society results in an uneven distribution of the benefits and the burdens of research. The IRB will closely examine research that selects subjects solely due to their easy availability, subordinate position, or susceptibility to manipulation (e.g., children, prisoners, decision-impaired, etc.).

The IRB will seek assurance that potential subjects are not coerced into participating in research, nor must they fear the loss of some benefit to which they are otherwise entitled if they choose not to participate. A person in authority, such as a supervisor recruiting co-workers, must take special precautions to ensure that a potential subject's decision to participate in research is not based on subtle pressures such as fear of a poor appraisal or loss of job.

Investigators proposing to recruit and select subordinates, students, or other co-workers as research subjects must justify the necessity for the inclusion of these individuals in the protocol. The LLNL IRB strongly discourages the recruitment of subordinates and will closely scrutinize the precautions that are put in place to prevent the appearance of coercion in the recruitment of these subjects. The protocol should clearly articulate how the recruitment will avoid the appearance of coercion when selecting subjects who are in a dependent relationship to the investigator.

2.6.3 Discussion of the Benefits and Risks

The research protocol must include a discussion of both the possible benefits and risks of the research. The investigator should consider only those risks and benefits that may result from the research. Evaluating the possible long-range effect of applying the knowledge gained through the research should not be included in this discussion. (See Section 2.8, "The Consent Process", for further discussion of risks and benefits.)

A realistic discussion of the benefits of research must take into account any possible benefits a subject might derive from participation in research that would justify asking a person to undertake the risks of the study. Payment for participation in research is not considered a benefit. As appropriate, a discussion of benefits should also include what the investigator expects to learn from the research, and what value it will have for the participant's community, the research institution, the funding agency, or science.

The discussion of risks must include inconveniences or discomforts and, where possible, an estimate of the likelihood and magnitude of harm. Biomedical research often presents some risk of physical injury to subjects. Although most of these risks are transient, some adverse effects of study participation (especially those resulting from medical procedures, drug research, or device research) may result in permanent injury to subjects. For all research with the potential to cause physical harm, investigators must list in writing all risk possibilities. As appropriate, the investigator should describe alternative methods that could have been used to minimize risk, stating why they were rejected. By clearly detailing procedures to address situations of physical harm, the IRB can be assured that the investigator has made efforts to minimize physical risks to the greatest extent possible.

Some research proposals involve the handling of sensitive information that may result in injury to subjects through a breach of confidentiality. These breaches may result in embarrassment within a subject's business or social group, loss of employment, or criminal prosecution. The IRB is especially concerned about information regarding drug and alcohol use, mental illness, sexual behavior, and illegal activities. For these situations, investigators must clearly detail strong safety precautions to ensure that the research does not cause social or economic risks to the subjects. Investigators might consider using Certificates of Confidentiality if the research would result in injury to subjects through a breach of confidentiality.

2.6.3.1 Privacy and Confidentiality Concerns

Privacy refers to a person's interest in controlling other's access to data about him/herself. Confidentiality is an extension of the concept of privacy; it refers to data (some record about the person, such as notes or a videotape of the person) and to how data are to be handled in keeping with the subjects' interest in controlling the access of others to information about themselves. Ideally, confidentiality is handled in an informed consent agreement between investigator and subject; the agreement states what may be done with private information that the subject conveys to the investigator. The terms of the confidentiality agreement need to be tailored to the particular situation.

Investigators are required to maintain and protect the privacy and the confidentiality of all personally identifiable information of all human subjects participating in research, except as may be required by law or released with the written permission of the subject. Subjects have the right to be protected against invasion of their privacy, and to expect that their personal dignity will be maintained and the confidentiality of their private information will be preserved. The more sensitive the research material, the greater the care required in obtaining, handling, and storing data.

Information through which subjects may be identified include their names, employee numbers, hospital ID numbers, social security numbers, driver's license numbers, home addresses, photographs, videotapes, and the like. Individuals also may be identified by description, for example, as the personnel manager in a particular company, the sixth grade teacher in a certain school, or the pediatric nurse at a local hospital. If information or data to be collected may be traced back to individual subjects, safeguards should be provided to ensure confidentiality.

Investigators will be asked by the IRB to describe how the data and links to subjects will be stored and maintained. They should also consider whether or not they will (1) provide information about subjects to others not involved in the research and (2) provide information they have learned about the subjects to the subject. Finally, investigators should consider to what extent a breach of confidentiality or invasion of privacy would constitute harm. If harm is a possibility, investigators must provide adequate provisions to protect participants from those harms and inform subjects of the possible harm.

Guidelines for protecting confidentiality

- *Limit recording of personal information to that which is essential to the research.*
- *Store personally identifiable data securely and limit access to the principal investigator and authorized staff.*
- *Code data as early in the research as possible, and when appropriate, develop a plan for the ultimate disposition or destruction of the code linking the data to individual subjects.*
- *Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available. (Contact the IRB Office for further information.)*
- *Do not disclose personally identifiable data to anyone other than the research team without the written consent of the subjects or their legal representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).*

2.6.4 Risk/Benefit Assessment

The IRB requests that researchers assess the relative weights of the study's risks and benefits in the protocol application. Important research may necessarily contain risk. Such research is acceptable if (1) it is well-designed, (2) it will contribute to generalizable scientific knowledge, (3) it is conducted by a competent investigator, and (4) risk/ benefit assessment and planning have occurred. The IRB will not approve studies in which the risks outweigh the benefits.

2.6.5 Financial Considerations for Subjects

Participation in research can lead to additional monetary costs for study subjects. Procedures billed to insurance companies may require a significant co-payment on behalf of the subjects: insurance companies may refuse to pay for "investigational" therapies, subjects may be responsible for transportation costs, and subjects may lose wages during research participation. Investigators should attempt to minimize any economic costs to subjects. If the research involves additional actual costs to individuals, the anticipated costs should be described to subjects during the consent process.

If subjects are to be paid for their participation in the research activity, the investigator should provide information regarding the total dollar amount that subjects will be paid for participation in the study, and should give any other relevant information such as pro-rating if a subject does not complete the study, or bonus payment at the end of the study. Subjects should not be required

to complete the entire study before receiving any reimbursement. Bonus payments for study completion should be modest.

If a protocol involves more than minimal risk, the IRB will require that the investigator provide appropriate information about any compensation and/or medical treatment that would be available if an injury or illness occurs. (See Section 2.8.2.2, "Basic Elements of the Consent Form", for further information regarding injury compensation.)

2.6.6 Disclosure of Investigator's Personal or Financial Interest in the Research Study and/or Sponsor[1]

The term "conflict of interest" in science refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research. The bias such conflicts may conceivably impart not only affects collection, analysis, and interpretation of data, but also the hiring of staff, procurement of materials, sharing of results, choice of protocol, and the use of statistical methods. Conflicts of interest are particularly important to consider in biomedical and behavioral research because of the impact such conflicts can have on human health.

It is not possible to completely eradicate the potential for conflict of interest because there are certain rewards that are inherent in the structure of the research enterprise. Such rewards may be completely unrelated to relationships with industry or private sponsorship. For example, positive research results may contribute to opportunities for publication, promotion, tenure, grant renewals, and so forth. In addition, positive results are often more gratifying and lead to greater personal satisfaction than negative outcomes. These influences are integral to doing business as a researcher and are indeed the motivating forces for diligent scientists. If abused, however, these influences can be as much a source of conflict in the search for truth as interests of a pecuniary nature. Such conflicts become detrimental when the potential rewards, financial or otherwise, cause deviation from absolute objectivity in the design, interpretation, and publication of research activities, or in other academic and professional decisions.

The mere appearance of a conflict may be just as serious and potentially damaging as an actual conflict. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts, therefore, should be evaluated and managed with the same vigor as known conflicts.

Some examples of problematic situations include investigators who:

- undertake basic or clinical research when the investigator or the investigator's immediate family has a financial, managerial, or ownership interest in the sponsoring company or in the company producing the drug/device under evaluation,
- accept gratuities or special favors from research sponsors, or

1. This section was adapted from the Association of American Medical Colleges "Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research", which was adopted by their Executive Council on February 22, 1990.

- enter into a consultantship arrangement with an organization or individual having an economic interest in related research.

Investigators should contact the IRB Office or the Laboratory's Conflict of Interest Coordinator if they have any questions or concerns regarding real or potential conflicts of interest with their research (http://www.llnl.gov/IPandC/Employee/interest.html).

2.6.7 Obtaining Informed Consent

In the past, it was generally accepted that written informed consent, obtained at a single contact between an investigator and a subject, was sufficient to meet legal and ethical obligations to patients and research subjects. This view was modified in the 1970s. Informed consent is now understood as an on-going process that starts with the initial presentation of a research activity to a prospective subject by the investigator and continues through the research activity until the subject ends his/her participation or the study closes.

Prospective subjects are rarely aware of research activities prior to an initial presentation by the principal investigator, or a member of the study team, and many subjects make their decision regarding whether to participate in the research at this point. As a result, it is critical that the initial presentation provide subjects with a clear understanding of the research, its procedures and attendant risks and benefits. Investigators are encouraged to provide sufficient time for a potential subject to reflect on the nature of participation during this important initial presentation of the research activity. When subjects are presented with numerous research and clinical options, the consent process should include a clear description of the possible ramifications resulting from each option presented. The presentation should not include specific "leading" information about whether to participate in any particular project.

Providing a potential subject with understandable information in the initial session will improve comprehension and enhance the potential for a more informed consent by the subject when agreeing to participate in the research.

The next phase in the consent process is the presentation of the Consent Form to subjects. According to federal regulations [45 CFR 46.117(b)], a Consent Form may be either of the following:

1. A written consent document that contains the elements of informed consent as described in Section 2.8.1, "Elements of Consent". This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator must give either the subject or the representative adequate opportunity to read it before it is signed.
2. A short form written consent document stating that the elements of informed consent as described in Section 2.8.1, "Elements of Consent", have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there must be a witness to the oral presentation. Also, the IRB must first approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign

a copy of the summary. A copy of the summary must be given to the subject or the representative, in addition to a copy of the short form.

When a written consent form is being used, the member of the study team who is obtaining consent should ask the subject if s/he understands the information contained in the form after the subject has read it. In situations where the ability of the subject to understand the form is in question (e.g., the form includes complex scientific information or the subject is possibly educationally or mentally challenged), the person obtaining the consent should ask questions of the subject to ensure an understanding of the basic elements of the Consent Form. An effective way to assess the subject's comprehension of the Consent Form is to request that the subject summarize the risks of participation, how the subject may withdraw, and what alternatives exist to participation in the research.

The consent process does not end with the signing of a consent form. Research is an on-going process that involves the constant re-evaluation of current information and procedures. It is important that investigators apprise subjects of new research information that may have an impact on the subject's willingness to continue participation in the study. Investigators should note, however, that the IRB must review and approve communications with subjects relating to their participation in the study prior to communicating that information to the subject.

In conclusion, it is difficult to be confident that volunteers truly understand the nature of their participation in research when they are confronted with complex scientific details in a brief and isolated consent session. By adopting the concept of an on-going consent process, subjects will have an improved understanding of the risks and anticipated benefits (to themselves, others, and society) as a result of their participation in the research. Creating an ongoing consent process will facilitate an exchange of information between subjects and investigators in an increasingly complex scientific environment. By providing subjects with the opportunity to give effective and on-going informed consent, in a process that incorporates the free exchange of information between both the investigator and the subject, investigators will be living up to the highest standards for the conduct of ethical research at LLNL.

2.7 Additional Considerations when Developing a Protocol

The basic elements for developing any protocol involving human subjects were discussed in the previous section. There are, however, specific areas of research that require additional consideration. The following topics are discussed in further detail in this section:

- Large-scale DNA sequencing
- Foreign collaborations
- FDA-regulated studies
- Inclusion of vulnerable populations in research
- Federally sponsored studies
- Use of surveys, questionnaires, or interviews
- Use of advertisements, press releases, or bulletin board announcements

- Studies involving toxic or other potentially harmful agents
- Studies involving human embryonic stem cells, germ cells, and cell-derived test articles

Researchers are encouraged to review the information provided in this section when first developing their research protocol. The IRB Office is always available to answer any questions investigators may have regarding these types of studies. To contact the IRB Office please use the following information:

IRB Office
7000 East Ave, L-448
Livermore, CA 94550
Phone: 925-422-8069
Fax: 925-422-8226
Email: dake1@llnl.gov
Office location: B3703, R1258

2.7.1 Large-Scale DNA Sequencing

The following list summarizes the guidelines of the DOE's National Human Genome Research Institute (NHGRI), regarding human subject concerns in large-scale DNA sequencing. (To review the complete guidance document, which was issued August 17, 1996, see the NHGRI Web site at http://www.nhgri.nih.gov/.)

- Those engaged in large-scale sequencing must be sensitive to the unique features of this type of research and ensure that both the protections normally afforded research subjects and the special issues associated with human genomic DNA sequencing are thoroughly addressed.
- For the foreseeable future, establishing effective confidentiality, rather than relying on anonymity, will be a very useful approach to protecting donors.
- Investigators should introduce as many disconnects as possible between the identity of donors and the publicly available information and materials.
- No phenotypic or demographic information about donors should be linked to the DNA to be sequenced.
- There are no scientific reasons why DNA donors should not be selected from diverse pools of potential donors.
- While the choice of donors will not be dictated to investigators, it is expected that, because multiple libraries will be produced, a number of them will be made from female sources while others will be made from male sources.
- Donors should be solicited broadly by using general announcements rather than by direct invitations to co-workers. This will reduce the likelihood of "undue coercion" by decreasing the influence of the employee/employer relationship.

- The disclosure process to potential donors must clearly specify what the process of DNA donation involves, what may make it different from other types of research, and what the implications are of one's DNA sequence information being a public scientific resource.
- Library makers are encouraged to establish a collaboration with one or more human genetics units (or tissue banks).
- The library maker should have no contact with the donor and no opportunity to obtain any information about the donor's identity.
- Projects to construct libraries for large-scale DNA sequencing must obtain IRB approval before work is initiated.
- Existing libraries can continue to be used for large-scale sequencing, only if IRB approval and subject consent for continued use are obtained and approval by the funding agency is granted.
- In obtaining informed consent for continued use of existing libraries, investigators must guard against coercion of the DNA donor.

2.7.2 Foreign Collaborations

Investigators and/or LLNL staff working on projects outside of the United States that employ humans as experimental subjects are responsible for obtaining copies of foreign approvals and other documentation necessary for LLNL IRB review. In addition, the investigator must assure the LLNL IRB that an ethics review board, fully constituted in the geographic vicinity of the actual work, has reviewed and approved the project, and that the major aspects of US federal regulations were observed. This means that:

- The cognizant foreign institution's ethics review board is comprised of members that were selected according to the U.S. federal guidelines for IRB membership.
- If the local language is other than English, the experimental protocol and documents that are provided to subjects (e.g., informed consent documents, recruitment materials, questionnaires, etc.) must be written in the appropriate language, translated into English, and included in the application packet to the LLNL IRB.
- Minutes of the meeting during which the protocol was approved are translated into English and forwarded to the LLNL investigator.
- Investigators must be knowledgeable and sensitive to issues, such as the expectations of the local volunteer population, the practices of the local collaborating experimenter(s), the meaning of informed consent, and possible coercion and enticement activities.
- The IRB Office must report all foreign-approved collaborations to the DOE.

> ***Note**: Human subjects research involving projects outside the United States are typically complex. Investigators are encouraged to contact the IRB Office as early as possible for assistance.*

2.7.3 Studies Involving Products Regulated by the Food and Drug Administration

The Food and Drug Administration (FDA) regulates all human subjects research involving drugs, medical devices, and biologics, including the ingestion or injection of radio-labeled compounds. FDA regulations require IRB review and informed consent (21 CFR parts 56 and 50, respectively) in much the same way that the DHHS or DOE do. However, the FDA has several additional reporting conditions that directly involve investigators.

If an investigator is the developer of the drug or device and no commercial manufacturer is involved, then either the investigator or the investigator's institution may be the sponsor for purposes of designing and organizing clinical trials. The sponsor is responsible for (1) submitting an investigational new drug (IND) or investigational device exemption (IDE) application to the FDA and (2) providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of investigators. LLNL employees contemplating the dual role of sponsor/investigator should consult with IRB Office staff about these additional responsibilities.

Clinical trials conducted under an IND or IDE issued by the FDA must adhere to the protocol as submitted by the investigator. Any modification (e.g., extension to another age group, use of a different dose, or change in subject eligibility criteria), must be approved by the FDA and the IRB prior to implementation, unless immediate action is required to eliminate apparent immediate hazards to human subjects. Any changes made to eliminate an immediate hazard must be reported to the IRB within five working days.

> ***Note**: Deviation from the approved protocol may subject the investigator to sanctions by the FDA and/or the IRB, and possibly also to charges of scientific misconduct.*

2.7.3.1 Sponsor–Investigator–IRB Interactions

Investigators are generally expected to provide the communication link between the IRB and a sponsor. Such linkage is agreed to by the sponsors and investigators when they sign forms FDA-1571 and FDA-1572, respectively, for drug and biologic studies or an investigator agreement for device studies. However, the regulations do not prohibit direct sponsor–IRB contacts. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. In those cases, the investigator will be kept apprised of the discussion.

FDA regulations require that a sponsor assure the FDA that a study will be conducted in compliance with the informed consent and IRB regulations (21 CFR 50 and 56). Sponsors, in turn, are expected to rely on the investigator who assures the sponsor, on form FDA-1572 for

drugs and biologics or the investigator agreement for devices, that the study will be reviewed by the investigator's IRB.

The IRB will notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity [21 CFR 56.109(e)]. The investigator should make this correspondence available to the sponsor, as this documentation provides the sponsor with reasonable assurance that the IRB has complied with 21 CFR 56 and that it will be responsible for initial and continuing review of the study.

A sponsor and/or investigator may reach an impasse with the IRB about study procedures or specific wording in an informed consent document. Any disagreements between a sponsor, the IRB, and an investigator should be resolved through appropriate communication among those parties, with the IRB having final say about what it will and will not approve. The FDA does not mediate such disagreements.

2.7.3.2 Types of FDA-Regulated Products

The FDA regulations include specific instructions for the content of records that must be created and maintained in clinical investigations of drugs and devices [21 CFR 312.62 (drugs) and 21 CFR 812.40 (devices)]. Please contact the IRB Office for additional information.

2.7.3.2.1 Medical devices

A medical device is defined, in part, as any health-care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, intra-ocular lenses, and orthopedic pins. Medical devices also include diagnostic aids, such as reagents and test kits for *in vitro* diagnosis of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the FDA's informed consent and IRB regulations. Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low-risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a premarket notification to the FDA. The FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendment device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and pre-market approval before it can be marketed unless it is reclassified into a lower regulatory class.

2.7.3.2.1.1 Device Classifications

In 1976, Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act gave the FDA the responsibility for assuring the safety and effectiveness of devices intended for human use. In implementing these Amendments, the FDA has classified devices according to their level of risk.

- **Class I devices**—devices for which safety and effectiveness can be assured so long as there is compliance with provisions for notification of defects, repair, replacement or refund, records, and reports. Device manufacturers are required to also avoid distribution of adulterated, misbranded, or banned devices.
- **Class II devices**—devices that require something more than proper labeling and quality assurance to ensure their safety and effectiveness.
- **Class III devices**—devices that are life-sustaining, life-supporting, implanted in the body, or of substantial importance in preventing impairment.
- **510(K) devices**—devices that are substantially equivalent to one marketed prior to the enactment of the Medical Device Amendments (1976). Such devices may be sold without additional proof of safety and efficacy under Section 510(K) of the federal Food, Drug, and Cosmetic Act. These devices are thus commonly referred to as "510(K)" devices. A sponsor planning to market the device must notify the FDA 90 days in advance of placing the device on the market. If the FDA agrees that the device is substantially equivalent to one already on the market, the device may then be sold without further research. Research activities involving a 510(K) device do not require an IDE, but do require approval by the LLNL IRB prior to the initiation of research.

  If the FDA determines that a new device is not substantially equivalent to a pre-amendment device, the new device is automatically designated a Class III medical device and the sponsor is required to obtain pre-marketing approval from the FDA. Studies conducted to develop safety and effectiveness data for such devices must be conducted according to the FDA requirements of Investigational Devices (21 CFR 812).

2.7.3.2.1.2 Investigational Device Exemptions (IDEs)

An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the IDE regulations (21 CFR 812). Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)].

Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "non-significant risk" (NSR). (Examples of each kind, published by the FDA, are included in Appendix 8.) The initial determination of whether a device is an SR or NSR is made by the sponsor. The proposed study is then submitted either to the FDA (for SR studies) or to the IRB (for NSR studies).

The IRB's SR/NSR determination has significant consequences for the study sponsor, the FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirement (21 CFR 812), and may not commence until 30 days following the sponsor's submission of an IDE application to the FDA. Submission of the IDE application enables the FDA to review information about the technical characteristics of the device, the results of any prior studies (laboratory, animal, or human) involving the device, and the proposed study protocol and consent documents. Based upon the review of this information, the FDA may impose restrictions on the study to ensure that risks to subjects are minimized and do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained. The study may not commence until the FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to the FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirement" of the IDE regulations [21 CFR 812.2(b)]. Unless otherwise notified by the FDA, an NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, record-keeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

Once the final SR/NSR decision has been rendered by the IRB (or the FDA), the IRB will determine whether or not the study should be approved, using the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111). Some NSR studies may qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure (21 CFR 56.110). However, the FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Additional information about device studies can be found on the FDA's Web site at http://www.fda.gov/cdrh/devadvice/11.html.

- **Studies involving NSR devices**—Investigators should clearly explain in their applications to the IRB why the sponsor believes the device presents no significant risk to study participants and provide supporting information, such as reports of prior investigations. The investigator should also inform the IRB whether the FDA or any other IRB has made a risk assessment and what the results of those assessments were. The IRB then will make an independent assessment of the risk of the investigational device to be used in the study. If the IRB agrees that the device poses no significant risk to research subjects, the investigator will not be required to obtain an IDE from the FDA to conduct the study. If the IRB instead believes that the device poses significant risk to research subjects, the investigator will be notified by the IRB. The investigator is then required to notify the sponsor of the IRB's decision within 5 business days, and the sponsor must then notify the FDA of the IRB determination. Investigations determined by the IRB to involve an SR device, will be reviewed according to the requirements described below. Following the IRB determination of the risk involved, the IRB will review the protocol to make a risk/benefit

assessment and consider the acceptability of the Consent Form, as described elsewhere in this document.

- **Studies involving SR devices**—Sponsors are responsible for making an initial risk assessment regarding an investigational device. An SR device, by definition, is an investigational medical device that presents a serious risk to the health or safety of the research subjects. Such a device is:
  - intended for use as an implant; or
  - purported to be useful in supporting or sustaining human life; or
  - intended for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
  - one that otherwise presents a serious risk to the health, safety, or welfare of subjects.

  Investigators should clearly explain in their protocol whether the sponsor believes that a device poses a significant risk to subjects when used in the context of the research activity, and if so, why. In addition, investigators should inform the IRB of results of any FDA or other IRB risk assessment of the device. Supporting information, such as reports of prior investigations or risk determinations, should be provided by the sponsor. The IRB will make an independent assessment of the risk of the investigational device to be used in the study. If the IRB agrees that the device poses significant risk to research subjects, the investigator will be required to obtain an IDE from the FDA to conduct the study. Following the IRB determination of the risk presented, the IRB will make a risk/benefit assessment and determine the acceptability of the Consent Form in accordance with normal review procedures (see Section 3.4, "IRB Review Process"). Additional information regarding how to obtain an IDE from the FDA can be obtained by calling the IRB Office at (925) 422-8069.

  When submitting a research protocol involving a medical device, the investigator must complete and attach Form HSR-6, "IRB Determination of Risk for Investigational Devices", and, when one exists, an Investigator's Brochure.

2.7.3.2.2 Investigational drugs

Research involving experimental or licensed pharmaceuticals is regulated primarily by the FDA and provides a transition from "promising" basic or laboratory research to "accepted" therapeutic or diagnostic procedures for patients. FDA guidelines for the investigational use of a new drug can be found at the following Web site:
http://www.fda.gov/cder/regulatory/applications/default.htm.

Investigational drugs include the following:

- Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA.
- Products that are already approved by the FDA as safe and effective for specific indications but are being studied for new indications (or doses, strengths, or frequency) other than those that have been approved (e.g., off-label use).

Federal law prohibits the distribution of new drugs until the FDA has reviewed clinical data, determined that a particular product is safe and effective for a specific use in human patients, and issued a pre-market approval. To test a new drug in clinical trials, the investigator must obtain an exemption from that law. Thus, a drug sponsor is required to apply for an Investigational New Drug (IND) exemption before tests with human subjects may begin.

The sponsor is required to wait for 30 days after the FDA receives the IND application, to permit FDA scientists to review the materials and, if necessary, request additional information, require modifications, or disapprove the application. The FDA notifies the sponsor of the date it receives the application. The LLNL IRB will not provide formal approval for a study until the 30 days have elapsed and the FDA has either provided an IND number or advised the sponsor that an IND is not required [21 CFR 312.40(b)].

If the investigator is the developer of the drug and no commercial manufacturer is involved, then either the investigator or the investigator's institution may be the sponsor for purposes of designing and organizing clinical trials. The sponsor is responsible for submitting an IND application to the FDA and providing a copy of the FDA's response to the IRB. Sponsors also have important administrative and reporting requirements above and beyond those of investigators. LLNL investigators contemplating the dual role of sponsor/investigator should consult with the FDA's Center for Drug Evaluation and Research (located at http://www.fda.gov/cder/) to better understand the considerable time and resources associated with sponsorship.

2.7.3.2.2.1 Types of Drug Trials

The FDA has defined 4 types of drug trials, ranging from initial investigations of new drugs conducted with healthy volunteers to post-market studies to delineate additional information about the drug's risks, benefits, and optimal use. Additional information about the four phases is provided below.

- **Phase 1 drug trials**—Drug trials that include the initial introduction of an investigational new drug into humans. Typically, these studies are closely monitored and conducted with healthy volunteers even when the drug is intended for use in patients with a particular disease. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.
- **Phase 2 drug trials**—Drug trials that include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored,

and conducted with a relatively small number of patients—usually no more than several hundred subjects.

- **Phase 3 drug trials**—Drug trials that involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit/risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient–subjects.
- **Phase 4 drug trials**—Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time. Research concerning new treatments for certain life-threatening conditions (e.g., cancer, AIDS, emergency-room interventions) may progress differently through the four phases. Investigators interested in studies involving such products should contact the FDA for further information.

2.7.3.2.3 Studies involving exposure to internal and external ionizing radiation

For research involving exposure to ionizing radiation from internal radionuclides or external radiation sources, the FDA regulations require that the research be reviewed and approved by a Radioactive Drug Research Committee (RDRC) as well as by the IRB. LLNL does not have an RDRC. Therefore, the actual dosing of radio-labeled compounds or otherwise exposing research subjects to ionizing radiation is not allowed on-site at LLNL. Exposing human research subjects to radio-labeled compounds or ionizing radiation must occur at a collaborating institution, and with the approval of that institution's IRB and their Radioactive Drug Research Committee (RDRC). The LLNL IRB will require copies of all documentation submitted to the collaborating institution's RDRC, as well as a copy of the RDRC approval letter. This documentation must be included in the application packet that is submitted to the LLNL IRB, and will be reviewed by members of the IRB's Sub-committee on Dosimetry and Toxicology prior to full-board review.

Any human research involving ionizing radiation requires that investigators use an IRB-reviewed and approved Consent Form. The Consent Form should clearly outline, in layman's terms, the quantity, significance, and risk, if any, of the radiation absorbed dose. The dose is usually compared with background radiation, the occupational exposure limit of 5000 mrem per year, or radiation doses received from familiar medical procedures (e.g., a chest x-ray). The explanation should be written in terms that are understandable to a person with an eighth grade education.

2.7.3.3 Emergency Use of an FDA-Regulated Test Article

FDA regulations allow for the emergency use of an investigational drug, biologic, or device when an individual is in an immediately life-threatening situation for which no standard acceptable treatment is available, and there is not sufficient time to obtain IRB approval for use of the FDA-regulated test article [21 CFR 56.102(d)]. Medical personnel faced with the need for the emergency use of an investigational drug, biologic, or device will do so only under approved Health Services procedures. The FDA does require that emergency use of a test article be reported to the IRB within 5 working days (21 CFR 56.104).

On occasion, a sponsor will agree to allow the emergency use of a test article, but requires "an IRB approval letter" before the test article can be shipped. Under this circumstance, and on a case by case basis, the IRB may provide a letter stating that the IRB is aware of the proposed emergency use and that the use appears to meet the requirements of 21 CFR 56.102 (d).

Notifying the IRB of the emergency use of an FDA-regulated product should not be construed as IRB approval for future use. If medical personnel anticipate there may be subsequent need for the investigational product, a research protocol should be submitted to the IRB for review and approval.

2.7.4 Inclusion of Vulnerable Subjects in Research

2.7.4.1 Children

California law identifies children as those who have not yet reached their 18th birthday (i.e., 0-17 yr). Investigators who intend to involve children in human subjects research should familiarize themselves with the federal regulations (45 CFR 46, Subpart D), which require "additional safeguards… to protect the rights and welfare" of children involved in research as they are "vulnerable to coercion and undue influence." Investigators are also encouraged to review Section 2.8, "The Consent Process", for information about obtaining assent from children.

Federal regulations allow the IRB to approve research involving children only if special provisions are met and the research falls into one of four categories, based on the degree of risk and benefit to individual subjects. Those categories are discussed in the following sections.

2.7.4.1.1 Research involving no more than minimal risk

When the IRB finds that no greater than minimal risk to children is presented, it may approve the proposal **only if** adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

2.7.4.1.2 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure but that the intervention or procedure has the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, the IRB may approve the research **only if** (1) the risk is justified by the anticipated benefit

to the subjects, (2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches, **and** (3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

2.7.4.1.3 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not have the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, the IRB may approve the research **only if** (1) the risk represents a minor increase over minimal risk, (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations, (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition, **and** (4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

2.7.4.1.4 Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

If the IRB does not believe the research proposal meets any of the requirements set forth above, it may still approve the application but **only if** (1) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, **and** (2) the Secretary of the DHHS, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, or law) and following an opportunity for public review and comment, has determined either:

1. the research, in fact, satisfies one of the conditions set forth above, or
2. the research satisfies the following conditions: (a) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (b) the research will be conducted in accordance with sound ethical principles; and (c) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

For further information and guidance regarding children as research subjects, investigators should carefully review the applicable federal regulations found in 45 CFR 46, Subpart D, "Additional DHHS Protections for Children Involved as Subjects in Research". Investigators should also review assent/consent requirements.

2.7.4.2 Pregnant Women and Fetuses

If it is possible that pregnant women and their fetuses may be involved in a study, the protocol should include an assessment of the advantages and consequences of their inclusion in the study. This type of research poses special concerns for the IRB.

The fetus is unique and yet has an inextricable relationship to the mother. A fetus cannot consent to participate as a research subject. In the early 1970s, Congress required that the National Commission for the Protection of Human Subjects study the subject of fetal research. The Commission, in its findings, did not define the "personhood" of the fetus; however, it did recognize the genetic heritage and vulnerability of the fetus and affirmed that it should be treated respectfully and with dignity, regardless of its life prospects. The Commission also affirmed the legitimacy and importance of fetal research for improving the health of fetuses both in the present and future. In 1975, the DHHS fully implemented the recommendations of the National Commission (45 CFR 46, Subpart B). The rule has been amended several times, most recently in 2001.

In addition to the general requirements for review of research by the IRB, prior research with animal subjects and, if reasonable, research with non-pregnant persons should form the basis of the risk/benefit assessment for fetal research. Investigators who propose research involving human fetuses are required to assure the IRB that they are seeking information not obtainable in any other fashion. There are three types of fetal research: (1) the study is directed toward pregnant women in which the fetus is indirectly involved in the research; (2) the study is directed toward the fetus; and (3) studies in which both the pregnant woman and the fetus are the subjects of the research activity.

The IRB may only approve in utero research when one of the following two criteria are met in addition to all other applicable institutional, federal, state, and local requirements:

1. The purpose of the research is to meet the health needs of the fetus and is conducted in a way that will minimize risk (e.g., a new technique for fetal transfusions for Rh incompatibility); or
2. The research poses no more than minimal risk to the fetus and the purpose of the activity is the development of important biomedical knowledge that is unobtainable by other means.

After lengthy review, the National Commission determined that there is no difference between the moral status of a fetus destined for abortion and that of a fetus that is expected to be carried to term. Therefore, only those research procedures that are acceptable for a fetus going to term may be performed in anticipation of abortion, to preserve the mother's right to change her mind about ending the pregnancy. To address the numerous concerns that are raised by research activities involving the use of fetuses, the federal regulations have provided the following clarifications in the areas of ex utero, in utero, and fetal tissue, as discussed below:

2.7.4.2.1 Research involving the fetus ex utero (neonate)

The federal regulations indicate that a neonate (delivered fetus) is viable if, in the judgment of physicians, it is likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. If the neonate is viable, the regulations for research involving children apply.

Federal regulations define a nonviable neonate as follows: "an expelled or delivered neonate which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered neonate is nonviable at a gestational age less than 20 weeks and weight less than 500 grams, a specific determination as to viability must be made by a physician in each instance." If a neonate is non-viable, 45 CFR 46, Subpart B applies to the research activity.

2.7.4.2.2 Consent for research involving fetuses in utero

Because of the father's continuing responsibility for his offspring, the consent of both parents generally is required for research involving the fetus. The consent of the father is not required, however, in the following circumstances:

- The research is designed to meet the health needs of the pregnant woman.
- The father is not competent.
- The father's identity or whereabouts cannot reasonably be ascertained.
- The father is not reasonably available.
- The pregnancy resulted from rape.

2.7.4.2.3 Research involving fetal tissue

The use of dead fetuses, fetal material, and the placenta is gaining considerable attention due to the lifting of a moratorium on federally funded research involving the therapeutic transplantation into humans of fetal tissue obtained from induced abortions, and from recent controversy over the use of fetal stem cells.

When the fetal tissue is derived from an abortion, the decision to terminate a pregnancy and the actual abortion procedures must be kept independent from the retrieval and use of fetal tissue. The timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research.

Fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman. However, the decision and consent to terminate pregnancy must precede discussion of the possible use of the fetal tissue in research and any request for such consent that might be required for that use. A woman's consent to donate fetal remains is sufficient for the use of fetal tissue. Consent should be obtained in compliance with state law and the Uniform Anatomical Gift Act.

Payments and other forms of remuneration associated with the procurement of fetal tissue are prohibited, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissue.

Potential recipients of fetal tissues, as well as research and health care participants, should be informed about the tissues in question. This information should be provided to the prospective subjects in the Consent Form.

The pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue. Anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team. Experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance should be prohibited.

2.7.4.3 Prisoners

Prisoners are considered vulnerable because they are in a restrictive, institutional environment that affords little opportunity for making choices, earning money, communicating with outsiders, or obtaining medical care. The National Commission for the Protection of Human Subjects found that prisoners often volunteer for medical research as a means of access to a competent medical examination, because health care is woefully inadequate in most prisons.

Because their autonomy is limited, prisoners may participate only in certain categories of research, and special precautions are needed to ensure that their consent to participate in the research is both knowing and voluntary (45 CFR 46.302). Prisoners may participate in the following kinds of research:

- Studies of the possible causes, effects, and process of incarceration and criminal behavior, if those studies present no more than minimal risk or inconvenience to the subjects.
- Studies of prisons as institutions, or of prisoners as incarcerated persons, if those studies present no more than minimal risk or inconvenience to the subjects.
- Research on conditions affecting prisoners as a class (e.g., research on hepatitis, drug addiction, sexual assaults, and other conditions more prevalent in a prison population than elsewhere), but only after the Secretary of DHHS, has consulted with experts in medicine, ethics, and penology and published a notice approving the proposed research in the Federal Register.
- Research on practices that are intended, and reasonably likely, to enhance the well-being of the subjects; however, if some of the prisoners will be assigned to control groups which will not benefit from the research, then the study must first be approved by the Secretary of DHHS, after consultation with appropriate experts, as described above.

2.7.4.4 Co-Workers

LLNL employees are vulnerable to perceived, even if not intended, pressures to appear cooperative and supportive of their supervisor's work. Potentially affected groups include office staff, lab technicians, post-doctoral fellows, students, and contractors. Various procedures have been suggested to reduce the possibility of unintended coercion, while still permitting these individuals to participate as subjects in research, and include:

- posting IRB-approved advertisements throughout the Laboratory to recruit subjects from a broad base of employees and contractors, and
- avoiding any personal solicitations of co-workers by investigators, or fellow co-workers.

The IRB does not encourage recruitment procedures that target employees from the investigator's own lab or office. The IRB, however, will consider requests to recruit co-workers on a case by case basis.

2.7.5 Studies Sponsored by Federal or State Agencies

Investigators must submit a complete copy of the federal or state grant/proposal to the IRB when requesting review of human studies. Some agencies do not require IRB review until the investigator has been notified that funding for the research is likely. Investigators should check with their sponsors for guidance. However, investigators are strongly encouraged to contact the IRB Office at the beginning of the protocol development process to avoid delays in receipt of funding.

2.7.6 Use of Surveys, Questionnaires, or Interviews (by Phone or in Person)

The IRB considers interviews, surveys, and questionnaires part of the experiment. They must therefore be reviewed and approved by the IRB prior to use. Normally this is done as part of the IRB's review and approval of the entire protocol, so investigators should assure that these accompanying documents are submitted to the IRB. Investigators may submit draft versions of these documents for the initial IRB review. The IRB, however, is required to review any subsequent modifications. If the IRB approves the protocol prior to the review of the finalized document, the investigator will receive an approval notice indicating that the surveys, etc. cannot be used until the final version has been reviewed and approved by the IRB. If a protocol requires an interview, the investigator must attach a script of the interview, including the introduction, questions, and closing comments.

Subjects assume that information requested in surveys, interviews, and questionnaires is relevant, necessary, and specific to the research project; they should not constitute "fishing trips." The IRB will expect that the investigator can clearly explain the necessity of each question to any subject or the IRB.

2.7.7 Use of Advertisements, Press Releases, or Bulletin Board Announcements

Many recruitment techniques are used to identify potential research subjects. Common recruitment techniques include the use of contact letters, flyers, posters, newspaper ads, and press releases. Television and radio spots, Web sites, and electronic mailers are also considered direct advertisements. All direct advertising must have IRB approval before being used for recruiting subjects. It is considered part of the informed consent and subject selection process. In this regard, all direct advertising must:

- be reviewed by the IRB for the information contained and the mode of communication,
- not be coercive or use undue pressures,
- not be misleading to subjects, and
- not overemphasize payment or overstate benefits.

2.7.8 Studies Involving Toxic or Other Potentially Harmful Agents

Careful consideration is required for the use of human subjects in research that involves exposure to potentially toxic materials or potentially harmful physical agents (e.g., laser or microwave radiation, noise, heat, etc.). To allow the LLNL IRB to fully evaluate the risks and benefits of the proposed work, investigators must submit detailed information documenting the expected exposure of subjects to these agents and must have their detailed dose calculations independently reviewed and validated. Any qualified independent party, within or outside the Laboratory, can perform this review. Members of the LLNL IRB Subcommittee on Dosimetry and Toxicology may be contacted to obtain assistance in identifying qualified people to perform these calculations. (Please contact the IRB Office for referral.) The investigator is responsible for the cost of this dosimetry review.

Documentation provided to the IRB must cover the following:

- The assumptions used in subject selection, the agent and quantity used, the route of exposure, the frequency or duration of exposure, any assumptions regarding the amount of material absorbed, and any personal protective equipment used.
- The calculations that yielded the estimated dose and the quantitative risk associated with the exposure, whenever possible.
- References to community or occupational standards and, where possible, common exposures.
- A statement that the reviewer has no direct involvement in the research.
- A brief (2- to 4-sentence) summary of the qualifications of the reviewer.

If the proposed subjects are employees of LLNL or a collaborating institution, and the proposed exposure is to chemical agents involving inhalation only, and for which there is an existing OSHA Permissible Exposure Limit or American Conference of Governmental Industrial

Hygienists Threshold Limit Value, the analysis may be based on exposure rather than absorbed dose.

The IRB recommends the following format for the independent report regarding the dosimetry/toxicology review. This report must be submitted in support of the application to use human subjects; proposals will not be considered until this review is provided.

To: Chair, Institutional Review Board,
Lawrence Livermore National Laboratory
Subject: Review of [Toxic Material/Physical Agent] Dosages in Support of IRB Protocol [Number], Titled [Title]

I have completed a review of the proposed exposure of human subjects to [toxic material or specific physical agent]. This review is based on assumptions provided to me by [name of individual providing information]. I have no personal interest or involvement in this experiment.

Assumptions: [State assumptions that form the basis for the calculations. This includes the nature of the subjects, exposure agent(s), the administered quantity, the route of exposure, and the duration or frequency of exposure. State any assumptions regarding the fraction of the exposure absorbed, unless this is provided in the calculations below. Describe any credit given for dose reduction by use of personal protective equipment or other mitigating factors.]

Calculations: [Show, in a clear way, how the anticipated dose to each agent is calculated. If any specialized software or protocol is used, note this.]

Standards: [Specify the exposure standard that is most applicable to the exposure described in this experiment.]

Comments and Discussion: [Include any comments that the reviewer believes germane to the review of the proposal. Include references to common exposures to provide a perspective of the risk, and discuss the potential consequences of exposure to health (if any). Provide a quantitative estimate of the risk, where possible.]

Independent Reviewer's Statement: [A brief (2- to 4-sentence) statement of the qualifications of the reviewer.]

Signature/Date

2.7.9 Studies Involving Human Embryonic Stem Cells, Germ Cells, and Cell-Derived Test Articles

In vitro research using cell lines that are already derived and established, from which the identity of the donor cannot readily be ascertained by the investigator, requires administrative review by the IRB Office. Please see Section 2.3, "Research Eligible for Administrative (Exempt) Review", for more information about administrative reviews.

Research using cell lines that allow identification of a donor, including cells that retain links to coded information that would allow identification of donors, is generally considered human subjects research and requires IRB review. However, if the investigator obtains a written agreement from the holder of the identifiable private information (e.g., the deriver of the cell line) such that information will not be released to the investigator under any circumstances, and that the research will be conducted within the terms of the applicable Assurance by all parties engaged in the research, the IRB may determine that an administrative review is appropriate. Investigators should contact the IRB Office for further information.

All human subjects research involving the use of cells derived from human embryos or fetal tissue (1) is governed by 45 CFR 46, (2) may be subject to FDA regulations, and (3) must have IRB review and approval.

Research involving the derivation of **new** human embryonic stem cells from human embryos cannot be conducted at LLNL. Research involving the derivation of human embryonic germ cells[2] from fetal tissue may be conducted at LLNL. Any research involving human embryonic germ cells derived from human fetal tissue must be conducted in compliance with the NIH "Guidelines for Research Using Human Pluripotent Stem Cells" (http://www.nih.gov/news/stemcell).

All research and clinical trials involving human transplantation of cells or test articles, such as differentiated cells derived from human embryos or human fetal tissue, must be conducted in compliance with FDA regulations and Public Law 103-43, "Research on Transplantation of Fetal Tissue". Further information can be found at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/publiclaw103-43.htm.

Clinical research trials involving the use of stem cells and stem cell derived test articles are subject to the FDA's IND regulations and all human studies conducted under INDs require IRB review of the clinical protocol(s). Investigators contemplating such trials should contact the Center for Biologics Evaluation and Review (CBER) at the FDA for specific advice regarding fulfillment of these requirements. CBER can be reached at (301) 827-5102.

2. "Germ cells" are defined as the self-replicating cells that develop into the primary germ layers—the ectoderm, mesoderm, and endoderm.

2.8 The Consent Process

As described in the Belmont Report, consent must be (1) informed, (2) understood, and (3) voluntary. These are the hallmarks of consent and provide respect for research subjects by honoring their autonomy. Informed consent is not just a form or a signature, but a process of information exchange that includes subject recruitment materials, verbal instructions, written materials, and question and answer sessions. The IRB and investigators share responsibility for ensuring that the informed consent process is adequate. Rather than an endpoint, the Consent Form should be the basis for a meaningful exchange between the investigator and the subject.

The Consent Form, or information sheet (an unsigned consent document), serves as a written summary of the exact information that is presented to a prospective subject. The investigator is responsible for ensuring that informed consent is obtained from each research subject before the subject participates in the research study. It also serves as a useful reference for both the subject and the investigator.

2.8.1 Elements of Consent

Federal regulations on informed consent stipulate eight basic required elements of consent, and note six additional elements that may be added to a Consent Form when appropriate. The IRB has developed a format (see Section 2.8.2, "LLNL's Standard Format for Consent Documents") that incorporates these informed consent regulations into a consent document. The consent document must present all necessary information to the prospective subject in as clear and easily readable a manner as possible.

2.8.1.1 Obtaining Consent

Investigators should give careful consideration to the process whereby consent is obtained. This should include considerations of how, when, and by whom consent will be obtained. Considerations regarding any special subject population should be addressed, as well.

2.8.1.1.1 Children

Federal law defines children as "persons who have not attained the legal age for consent… under the applicable law of the jurisdiction". In California, the legal age for consent is 18. When a child is the subject of research, the IRB must determine whether adequate provisions are made for soliciting the assent of the child, as well as the permission of the child's parent or court-appointed guardian. Assent and permission are defined as follows:

> **Assent**—a child's affirmative agreement to participate in research. Failure to object, absent affirmative agreement, should not be construed as assent. In general, children under the age of 7 are considered incapable of providing assent. Children between the ages of 7 and 12 are generally considered capable of providing assent, depending on the nature of the research and the individual child's maturity and psychological state. The assent process for children in this age group should be simplified so it is comprehensible to the children.

Children who are at least 13 years old can generally provide assent in a full and meaningful way.

In California, a child remains a minor until age 18 or upon marriage. Pregnancy does not confer adult status. The regulations permit children, with IRB approval, to consent on their own behalf if the research involves a treatment for which a child's consent is permissible under applicable law (e.g., use of contraceptives, treatment for venereal disease or drug abuse). If a subject under the age of 18 is legally emancipated, he/she may consent to participate in research without the permission of a parent or guardian.

The child's assent is required in all research where the subject has the capacity to comprehend aspects of the study. The assent process assures an element of understanding, cooperation, and a feeling of inclusion on the part of the child and also illustrates the investigator's respect for the rights and dignity of the child in the context of research. Investigators should remember that a child's mere refusal to object to participation in research should not be construed as assent. Out of respect for children as developing persons, they should be asked whether or not they wish to participate in the research, particularly if (1) the research does not involve interventions likely to benefit them and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

Parental permission—Current regulations tend to avoid the term "consent" when one person grants approval for another to participate in research. Parents or legal guardians therefore grant "permission" for children to participate in research (45 CFR 46.408). The "permission" form is, in essence, a consent document and should follow all applicable requirements for informed consent as outlined in this manual.

Whenever possible, the permission of both parents should be obtained; however, current federal regulations do not require permission from both parents in all research situations. In general, the risk to the child and the prospect of direct benefit for the child as a research subject determine whether single parental/guardian permission may be permitted. If the research involves no greater than minimal risk, permission of only one parent is sufficient [45 CFR 46.404]. If the research involves greater than minimal risk, consent of both parents must be obtained unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has the legal responsibility for the care and custody of the child [45 CFR 46.408(b)]. Investigators should obtain written permission from the parent/guardian prior to contacting a child for participation in research.

2.8.1.1.2 Non-English speaking subjects

If the study will include non-English speaking subjects, investigators should discuss the use of translators in the consent process and a copy of the translated Consent Form or information sheet should be submitted with the application.

2.8.1.1.3 Subjects unable to consent for themselves

For studies involving subjects who cannot give signed or even verbal consent for themselves (e.g., young children, mentally handicapped persons, unconscious patients) the IRB may waive this requirement if sufficient justification for use of the particular subject group is presented and if appropriate measures for obtaining consent from a legally authorized representative or a relative and/or subject advocate are followed. OHRP has reminded the IRBs of the mandate for obtaining legally effective informed consent prospectively from each research subject or the subject's legally authorized representative. California law does not allow for the waiver of consent in emergency research settings.

2.8.1.2 Waiver of Informed Consent

Written informed consent is a basic principle in the protection of human subjects, therefore, federal regulations allow the IRB to waive or alter the requirements only under extraordinary conditions. As a result, waivers of informed consent are one of the most misunderstood provisions of the federal regulations. There is often confusion as to whether an investigator is requesting a waiver of documentation of informed consent or a waiver to all or part of the consent process.

The IRB may only grant a waiver of or modification to the informed consent process by a vote of the full Board. Therefore, the IRB may not approve a request for waiver or modification of the informed consent process through the process of expedited review.

Also, according to the University of California Counsel memorandum dated December 20, 1996, California law does not allow for a waiver of written informed consent in emergency situations.

2.8.1.2.1 Waiver of documentation of informed consent

The federal regulations allow the IRB to waive the requirement for the investigator to obtain a signed consent form if it finds that either (1) the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

If an investigator requests a waiver of signed consent, then the application must provide a written justification for doing so.

As the federal regulations note, "in cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research." The IRB often requires the use of such a written statement, in the form of an information sheet, that includes most or all of the same elements as a consent form but does not require the signature of the subject.

2.8.1.2.2 Waiver or alteration of informed consent

The IRB may approve a consent procedure that does not include or that alters some or all of the elements of informed consent, or waives the requirement to document informed consent provided one of the following sets of conditions exists and is documented:

1. The research or demonstration project is conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (a) programs under the Social Security Act, or other public benefit or service programs, (b) procedures for obtaining benefits or services under those programs, (c) possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs, and (d) the research could not practicably be carried out without the waiver or alteration.
2. The IRB may also grant a waiver if the research meets all of the following conditions: (a) the research involves no more than minimal risk to the subjects; (b) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and (c) the research could not practicably be carried out without the waiver or alteration and, whenever appropriate, the subjects will be provided with additional pertinent information after participation.

> ***Note:*** *Federal regulations do not allow a waiver of informed consent because conditions make it difficult to enroll subjects into the research.*

2.8.1.3 Use of a Collaborating Institution's Consent Form

In some cases, an LLNL investigator may wish to conduct research that will be carried out at another study site where that site's institutional review board has different standards for consent documentation. In such cases, the LLNL IRB will consider a request to approve use of the other IRB's approved Consent Form or information sheet, as long as it satisfies the federal requirements for informed consent. Additionally, the LLNL IRB expects that collaborators will note LLNL's involvement in the study, usually under the section on the purpose and background of the study.

2.8.1.4 Deception or Withholding Information

Special considerations are required when deception or incomplete disclosure is an integral part of the research. The requirements for complete informed consent strongly favor comprehensive, honest, and understandable disclosure of all elements of the subject's participation in research. There are times, however, when investigators plan to withhold information about the real purpose of the study or purposely give subjects false information about some aspect of the research. As a result, subjects cannot prospectively give fully informed consent. Minor deception, such as withholding specific points of interest in an attempt to prevent a bias in the results can be acceptable, provided the subject is fully debriefed after participation. Risks stemming from major deception, such as leading a subject to believe that s/he has committed a

crime or has a disease, are more problematic and must be clearly counterbalanced by the benefits of the research.

> ***Note:*** *Incomplete disclosure or the use of deception* ***cannot*** *be used as a means to secure the participation of subjects in research. The IRB will not approve research that entails more than minimal risk and withholds information that is material to the subject's decision to participate in the study.*

For the IRB to adequately review the research, investigators should justify, in detail, in the protocol, the reasons for deceiving or withholding information from subjects, including an explanation of (1) the necessity for deceiving subjects, (2) how the potential benefits of the research justify the use of deception, and (3) how the investigators will conduct the debriefing. In addition, investigators should include a debriefing script or statement that indicates the information subjects will receive regarding their participation in the research.

2.8.2 LLNL's Standard Format for Consent Documents

Whenever a consent form or an information sheet is to be used, the following format should be followed, with adaptations as appropriate. Though variations may be accepted, provided that all required elements of consent are included, the following format is recommended and preferred by the IRB. This format was developed to (1) satisfy federal and institutional informed consent requirements and (2) encourage the construction of a consent document that presents all necessary information in a clear and easily readable manner.

2.8.2.1 General Information

Delays in IRB approval commonly result from the submission of an inadequate consent form. The following guidelines are meant to assist you with the basic format of your consent form.

- **Eighth-grade reading level—**The primary goal of a consent form is to provide all required information about a study in language and format that is easily comprehensible, and presented at the most likely level of understanding of the subject population. For most studies, the consent form should be written at an eighth-grade reading level. Everyday vocabulary and simple sentence structure should be used throughout the form.
- **Lay language—**Unless the subjects are themselves medical professionals, scientific or technical terms should either be replaced with or defined in lay language. For example, "blood draw" is preferable to "venipuncture" and "x-ray" to "radiograph".
- **Non-legalistic language—**Legalistic sounding language such as "You hereby agree," "You certify that," "You, the undersigned, do acknowledge that", should not be used. Also, any phrases similar to the following should not be used: "You understand that," "You realize that," "You have been told that," "It has been explained to me that". Not only do these phrases not ensure a subject's comprehension but they lend the appearance of a legal document to the consent form.

- **Consistent use of person—**The person in which the form is written should be used consistently throughout. The IRB recommends that the form be written in the second person of the subject, that is, "You have been asked to participate in a research study."
- **Page numbering and date—**As a record-keeping aid for the study subjects, the IRB members/staff, and the investigators, each page of the consent form should be numbered (preferably "1 of 2," "2 of 2"). In addition, the lower corner of each page of the consent form should include the date of this version of the consent form.
- **Correct spelling and grammar—**The entire form should be carefully proofread for correct spelling and grammar before it is submitted to the IRB for review.

2.8.2.2 Basic Elements of the Consent Form

Reference to LLNL, and that a research project is being discussed, should be included in the consent form heading. For example:

LAWRENCE LIVERMORE NATIONAL LABORATORY
CONSENT TO BE A RESEARCH SUBJECT
or,
LAWRENCE LIVERMORE NATIONAL LABORATORY
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

The study title must be included in the heading of the form. If the official title is technical and difficult to understand, a simplified non-technical title should be used in addition to the official title. The IRB protocol number is not required but may be included in the heading or the footer.

If a study has more than one consent form, each form should be labeled or titled appropriately, and the same references used within the protocol.

2.8.2.2.1 Purpose and background

This section should present the introduction to the study, indicating who is conducting the research, stating the aim of the study, giving a brief summary of the background or reason for the project, and explaining why the individual has been asked to participate. The reason a person has been asked to participate should be simply but specifically stated (e.g., "because you have periodontal pockets around your teeth," "because you are a healthy person") and should not include a discussion of the inclusion/exclusion criteria. If an investigational device is being used in the study, this should be mentioned in this section and the device should be named.

This section should **not** begin with phrases similar to "You agree to participate" because the prospective subject has not yet had a chance to read the form, and could not yet make an informed decision about whether or not to participate. Rather, this section should indicate that the individual is being "asked", rather than "chosen" or "invited" to participate, because words like "chosen" or "invited" have connotations that are not necessarily those associated with being a participant in a research study. By the same token, if the study involves an investigational device, this should be referred to as "investigational" or "experimental" rather than "new," because the word "new" implies that something is automatically better.

2.8.2.2.2 Procedures

Each procedure should be listed, preferably in the order in which it occurs, and discussed in a separately numbered paragraph. If the study involves screening procedures, these should be mentioned first and identified as tests that will determine eligibility to participate in the study. This section should clearly state what will be done to the individual as a result of participation in the study, and, where appropriate, how this differs from standard treatment or what would happen to the individual if he/she did not participate in the study.

If a standard medical procedure is being done as part of the study, it should not be referred to as "standard" or "routine," because this could easily imply that the procedure would be done anyway for clinical reasons. Rather, what should be conveyed is that this procedure is an extra laboratory test that is commonly done for clinical purposes, but is being done here for research purposes.

Amounts of blood or tissue to be taken for study purposes should be specified using lay equivalents (e.g., teaspoons, ounces) for metric terms.

The number of times a procedure will be done, the time involved for each procedure, and the total amount of time for participation in the study should be specified. The location(s) where the procedures will be done should also be stated.

2.8.2.2.3 Risks and/or discomforts

The risks and/or possible discomforts of all study procedures should be listed and explained in this section. It is best to describe the risks of each procedure in a separate point and arrange them according to severity and the likelihood of occurrence. Where appropriate, the precautions that will be taken to avoid certain side effects or outcomes from occurring should be indicated and what will be done should they occur. The following four risk elements should be discussed, as appropriate:

1. **Likelihood of risks—**To the extent possible, consent forms should characterize the likelihood of risks using words like "likely," "frequent," "occasional," and "rare". When using these words it might be helpful to define them using percentages. For example, "likely" risks could be expected to affect more than 50% of subjects; "frequent" risks could affect 10–50% of subjects; "occasional" events could affect 1–10% of subjects; and "rare" events would affect less than 1% of subjects. Because of the difficulty of quantifying risks, and because consent forms should emphasize the most important risks as well as the most frequent risks, the exact wording and organization of the discussion of risks must be adjusted for each individual study.
2. **Injuries resulting from participation in a study**—Another risk for any biomedical study is that of injury due to participation in the study. If a protocol involves more than minimal risk and human subject contact is initiated by the LLNL investigator, then the consent form must contain an explanation of any compensation and/or medical treatment that would be available if an injury or illness occurs. The following examples are provided as guidance only. Injury compensation statements on consent forms for greater than minimal risk studies will be reviewed by the Board on a case-by-case basis.

Example 1: *The University of California will provide to any injured subject any and all standard medical treatment reasonably necessary for any injury or illness that a human subject suffers as a direct result of participation in an authorized University activity covered by University policy on the protection of human subjects in research or reimburse the subject for the costs of such treatment except when the injury or illness is a consequence of a medical research procedure that is designed to benefit the subject directly. For further information about this, please call the IRB Office at (925) 422-8069.*

Example 2: *If you are injured as a result of University employee negligence or misconduct, you may submit an administrative claim to the LLNL Risk Manager and pursue your remedies at law. The University will not provide free medical treatment or any other form of remedial compensation if University employees have conducted themselves properly and have not acted negligently during this experimental process.*

If a greater than minimal risk protocol includes research subjects who are also LLNL employees, the PI should include the following statement on the consent form:

Example 3: *In the event of an injury or illness incurred by you as a result of your participation in the experiment, you will be covered by LLNL Worker's Compensation. For further information about this, call the Institutional Review Board Office at (925) 422-8069 or write: Institutional Review Board Office, Lawrence Livermore National Laboratory, P.O. Box 808, L-448, Livermore, CA 94550.*

The following example is appropriate for greater than minimal risk protocols that are industry-sponsored (Work for Others, CRADA, etc.):

Example 4: *If you are injured as a result of being in this study, standard medical treatment will be available. The costs of such treatment may be covered by the University of California or by the study sponsor, [sponsor's name], depending upon a number of factors. The University and the sponsor do not normally provide any other form of compensation for injury. For further information about this, call the Institutional Review Board Office at (925) 422-8069 or write: Institutional Review Board Office, Lawrence Livermore National Laboratory, P.O. Box 808, L-448, Livermore, CA 94550.*

Note: *If the industry sponsor's indemnification policy is different from LLNL's and/or the industry sponsor does not wish to include its name in the LLNL injury compensation statement, then other options are available. The sponsor's name may be deleted entirely from the injury compensation statement or a brief paragraph may be added below and separate from the LLNL statement informing the subject of the sponsor's policy. Please note, however, that any description of the sponsor's policy should state what the sponsor will cover, not what it will not cover. Additionally, a sponsor's statement should not make reference to third party carriers, government programs, or lost wages.*

3. **Privacy and confidentiality—**Because one of the risks of participating in research is a loss of privacy, a discussion of confidentiality issues should be included in the Risks section. The confidentiality discussion should begin with this statement: "Participation in research will mean a loss of privacy." The consent form may then proceed to briefly describe how the confidentiality of private information will be protected, i.e., coding of records, limiting access to the study records, not using any individual identifies in publications or reports resulting from the study.

   For studies involving FDA-regulated products, officials from the sponsoring company and the FDA have at least some limited right to review individual records; subjects in such studies must be forewarned about this intrusion into their privacy.

   For all statements regarding confidentiality of research records, keep in mind that there is no legal privilege between investigator and subject like the one between physician and patient or counselor and client. Thus, a guarantee of complete confidentiality, or "strictest confidentiality," should not be given or implied. One should always state instead that confidentiality will be protected "as far as is possible" or "as far as is possible under the law."

> **Note:** *The one way to protect research records from subpoena is through a Federal Certificate of Confidentiality. More information about this Certificate may be obtained by contacting the federal funding agency or by calling the IRB Office. If such a certificate is obtained, it is recommended that the consent briefly discuss the added degree of protection that this certificate provides.*

4. **New information—**Federal regulations require the inclusion of a separate statement indicating that if new information that may affect a subject's willingness to continue participation (e.g., changes to the risk/benefit ratio or new alternatives to participation) develops during the course of the study, the subject will be promptly informed and may then decide whether to continue participation in the study. The IRB will advise the investigator whether or not subjects should be asked to sign a revised consent form containing the new information.

2.8.2.2.4 Benefits

Any potential direct benefits to the subject should be described first, followed by potential general benefits (e.g., to the group of subjects to which the individual belongs, to medical knowledge, etc.). The IRB recommends that a description of possible direct benefits be qualified with the phrase, "...but this cannot be guaranteed." If there is no direct benefit to the subject anticipated from the study, this should be stated at the beginning of the section.

The FDA recommends that possible benefits such as medical or societal benefits resulting from a research study be considered separately from payment for participation in the study. The IRB has adopted this recommendation. Thus, the discussion of payment or reimbursement should be

separate from the benefits statement and placed in the section addressing financial considerations.

2.8.2.2.5 Alternatives

The section should discuss any alternatives to participation in the study. This can be a short statement, but it should make clear the possible choices (e.g., no participation, or some or all of the protocol treatment, but without participation in the study, etc.) that are available if the individual chooses not to participate in the study. If the study involves only normal, healthy volunteers, and thus the only alternative is to decline participation in the study, this need not be mentioned in a separate section because the individual's right to choose not to participate will be made clear in the last section of the form.

2.8.2.2.6 Financial considerations

2.8.2.2.6.1 Costs/Financial Considerations

When participation in the study may result in any costs whatsoever to the subjects, clear information must be provided in the consent form regarding these costs. It there are no costs to the subject, this should be clearly stated as well.

If any real or potential financial conflicts of interest have been identified regarding the research activity, that information, as it affects the subject's decision to participate, should be included in this section.

2.8.2.2.6.2 Reimbursement/Payment

When referring to money that subjects will receive in return for participation in a study, either "reimbursement" or "payment" may be used. However, the term "compensation" should not be used because it is used on consent forms to designate compensation for injury. Investigators should avoid connotations of undue influence to participate or that the subject is being employed by the investigator. Rather, the sense should be that subjects will be reimbursed for their time, travel expenses, and the inconvenience of being a research subject.

This section should state the total dollar amount that the subject will be paid for participation in the study, and should give any other relevant information such as pro-rating if a subject does not complete the study, or bonus payment at the end of the study. If appropriate, a payment schedule should be included in this section. Subjects should not be required to complete the entire study in order to be reimbursed and bonus payments for study completion should be modest.

Subjects should be informed how payment will be made (e.g., in cash, by check) and when they will be paid (e.g., immediately after the interview, approximately six weeks after individual completion of the study). It is important that this information be clear and complete.

Payments for research participation in excess of $600 per calendar year are considered taxable income. If subjects will be paid more than $600, the Reimbursement section should explain that LLNL will request the subject's Social Security number in order to report this income to the IRS.

If there will be no payment or reimbursement to subjects for study participation, this information should be stated in this section.

2.8.2.2.7 Questions

This section should provide contact information for the subject in case of questions about the study. The principal investigator's name and phone number must be included in this section as subjects often wish to contact the person who is supervising the project. Blank lines to be filled in later may be included for additional contact persons. If the person explaining the study and obtaining consent is not the principal investigator, the blank lines in this section may be filled in with that person's name, and telephone number, if different, at the time consent is obtained.

2.8.2.2.8 Consent

There are three aspects of consent:

1. **Receipt of consent form and experimental subject's Bill of Rights**—This section should state that the subject has been given (not just offered) a copy of the Consent Form and, if it is a biomedical study, a copy of the Experimental Subject's Bill of Rights. The current LLNL version of the Bill of Rights should be attached to the consent form.

   While California law requires that the Experimental Subject's Bill of Rights be given only to subjects of biomedical research, IRB contact information is given in the LLNL Bill of Rights that subjects in all types of studies should receive. Therefore, for non-biomedical studies, either the Bill of Rights should be given to each participant, or the paragraph with the IRB contact information should be included in the consent form.

2. **Voluntary nature of participation in research**—This section should state that participation in research is voluntary, and explain the individual's right to decline to participate, or withdraw from the study at any time. If the subjects are patients, students, or employees, a phrase may be added indicating that refusal or withdrawal will be without jeopardy to status or career.

   The investigator may also wish to advise subjects that they may be withdrawn from the study if the investigator deems it in the best medical interests of the subject or for other reasons that should be specified (e.g., failure to keep appointments).

   Because communicating the voluntary nature of consent is so important, the IRB recommends that the statement to that effect be in capital letters, and the section be placed at the end of the form, near the signature section, for emphasis.

3. **Consent to participate**—In this section, the Board usually discourages wording such as "You have read this form and understand it; based on this understanding, you hereby agree to participate," because this does not guarantee an individual's comprehension, legally or otherwise. Rather, it is recommended that investigators simply state that if the person wishes to participate in the study, he or she should sign the form; signature will then indicate agreement to participate.

2.8.2.2.9 Signature section

Provide the following signature lines, as applicable, at the end of the Consent Form:

- **Signature of subject**—Unless a waiver of signed consent (i.e., use of an Information Sheet rather than a Consent Form) is approved by the IRB, this should include lines for the subject's printed name, his or her signature, and the date of signature.
- **Signature of person obtaining consent**—To provide subjects with a record of who explained the study to them, the consent form should include a signature line for the specific individual obtaining consent. In signing on this line, the individual is attesting that the requirements for informed consent have been satisfied.
- **Third-party signatures**—If the study involves subjects who cannot give consent for themselves, and the IRB accepts the justification for their inclusion in the study, a separate, appropriately worded and labeled signature section must be added to the Consent Form. For studies involving minors, this signature line will be for the parent(s) or guardian(s). In other studies where a legally authorized representative will give consent for the subject, an appropriately labeled signature line should be used.

2.8.2.3 Additional Elements of Informed Consent

Per 45 CFR 46.116(b), several additional pieces of information are required when, in the judgment of the IRB, they are appropriate. These additional elements are as follows:

- a statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
- any anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- any additional costs to the subject, or their insurance carrier, that may result from participation in the research;
- the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- a statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and
- the approximate number of subjects involved in the study.

2.9 Ongoing Responsibilities After Initial Protocol Approval

After a protocol has been approved by the IRB, the investigator has several on-going reporting responsibilities to the IRB. Those responsibilities are listed below.

2.9.1 Reporting Adverse Events

2.9.1.1 Injuries, Illnesses, or Other Unanticipated Complications Possibly Resulting from the Research

Any potentially serious, unanticipated complications affecting a subject require immediate reaction by the investigator to help mitigate the harm suffered and prevent further harm. In addition, investigators are responsible for reporting to the IRB Chair any injuries, illnesses, or other unanticipated complications possibly related to the research. This reporting must take place within 10 calendar days of the occurrence.

2.9.1.2 Unanticipated Problems or Non-Compliance with the Requirements of the Protocol

Investigators are responsible for reporting to the IRB Chair any unanticipated problems or noncompliance with the requirements of the approved protocol within 10 calendar days. The Chair may choose to discuss these matters at a meeting of the full Board.

2.9.2 Making Modifications to Currently Approved Research

All modifications to currently approved research must have IRB review and approval prior to implementation. Investigators should submit a "Request for Modification or Amendment" form and, as appropriate, the revised protocol, consent form, recruitment materials, etc. Investigators should highlight or use bold font to indicate where changes or additions have occurred on the revised documents.

2.9.2.1 Minor Modifications to Currently Approved Research

A minor modification is defined as a change that (1) would **not** materially affect an assessment of the risks and benefits of the study or (2) does not substantially change the specific aims or design of the study. Minor changes that do not increase the risk to research subjects may receive an expedited review.

Examples of minor modifications include:

- an increase or decrease in proposed human research subject enrollment,
- alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant,
- a decrease in the number or volume of biological sample collections, provided that such changes do not affect the collection of information related to safety evaluations,

- changes to improve the clarity of statements or to correct typographical errors, provided that such changes do not alter the content or intent of the statement,
- a change in principal investigator or the addition or deletion of qualified investigators, and
- the addition or the deletion of study sites.

2.9.2.2 Major Modifications to Currently Approved Research

A major modification is defined as a change that materially affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study. Major modifications to approved protocols that may increase the risk to subjects require a full board review.

2.9.2.3 Approval Period for Modifications

The IRB may only approve modifications submitted during a current approval year to the end of that period. For example, if the new or annual review takes place on January 1, 2002, the protocol will have an expiration date of January 1, 2003. If a modification is approved during this time, the expiration date still remains January 1, 2003. All modifications, amendments, and, when applicable, informed Consent Forms should be incorporated into the renewal application for IRB consideration during the annual review.

2.9.3 Continuing Review After Initial Application Approval

The IRB must conduct continuing review of protocols at intervals appropriate to the degree of risk, but not less than once per year. It is the investigator's responsibility to ensure that the research is reviewed on or before expiration of the current approval period, even if the research activity did not begin until some time after the IRB gave its initial approval. As a courtesy, investigators will be notified by the IRB Office six to eight (6–8) weeks prior to expiration of their IRB approval. An application for continuing review must be received by the IRB Office in time for review and approval in advance of the expiration date (3–4 weeks recommended).

Continuing review and approval is also necessary if recruitment of subjects stops but previously enrolled subjects continue to participate in the research or the study is in data analysis at LLNL.

2.9.3.1 Submitting a Renewal Application

In the renewal application, investigators should incorporate all of the addenda and modifications submitted to and approved by the IRB during the previous approval period. In addition to describing changes in the research design, number of subjects, or changes in Consent Form, the following information should also be included in the renewal request:

- an updated abstract of the study,
- the number of subjects seen since the last renewal, the total number to date, and the number of additional subjects yet to be recruited,
- the study status, if subject enrollment is complete,

- any adverse events during the past year,
- a determination of whether or not the risk/benefit assessment remains the same,
- a summary of results and publications, and
- plans for the coming year.

Consent Forms and other supporting documentation must also be reviewed by the IRB each time the protocol is updated. If the research activity involves a collaborating institution, a copy of the other institution's current IRB approval letter is also required.

> ***Note**: There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. Extensions beyond the expiration date will not be granted. If the IRB does not re-approve the research by the specified expiration date, subject accrual and research activities must be suspended pending re-approval of the research by the IRB.*

Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. If the investigator is actively pursuing renewal with the IRB and the IRB finds that it may be in the best interests of already-enrolled subjects' safety to continue with study treatments and procedures, the IRB may allow continuation of treatment for already-enrolled subjects during the time required to complete the review process.

2.9.3.2 Termination for Failure to Obtain Continuing Approval

The IRB has the authority to terminate or suspend approval of research that is not being conducted in accordance with regulatory and LLNL requirements regarding continuing review. When study approval is terminated by the Board due to lack of compliance with continuing review requirements, in addition to stopping all research activities, any subjects currently participating should be notified that the study has been terminated.

2.9.4 Maintenance and Retention of Records and Consent Forms

During the study, all documents, electronic files, videotapes, etc., that contain the subject's personal identifiers must be kept in locked storage with access restricted to the investigator and/or designee(s). Access restrictions must continue even after the study is completed and the records must be shipped to LLNL record storage facilities.

At a minimum, investigators must maintain research records for at least three (3) years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of the IRB, the federal department or agency supporting the research, and sponsor, if any. Beyond three (3) years, requirements for record retention vary with the type of research conducted, the provisions of the investigator's funding source, and LLNL

requirements. It is the investigator's responsibility to clearly understand the retention requirements of LLNL and/or their sponsor.

Based on current DOE direction, research records (including Consent Forms) involving ionizing radiation experiments on human subjects, or epidemiological studies of LLNL or any other DOE facility workers, must be retained until further notice.

Research records involving ingested, inhaled, or injected materials (other than ionizing radiation) that could represent even a small increase in risk to subjects (or are commonly but erroneously thought to increase such risks) are to be retained until the youngest exposed subject could reach 100 years of age.

Other human subjects records are to be retained in accordance with LLNL's record retention schedule for Medical Research and Development, Schedule Code 12-03-017, 12-03-018, and 12-03-019.

When human subjects records are sent to LLNL records storage, they should be clearly identified according to the categories identified above. For example, if the records involve ionizing radiation, the records transmittal form should indicate: "These are human subjects research records involving ionizing radiation; these records are under a DOE moratorium on destruction."

There should also be an accompanying memo identifying those individuals who have authorized access to the records. If the records reveal the identity of the individual subjects, the access should be limited to the experimental investigators and, if none of the investigators are then still employed at LLNL, access should be only with the approval of the Chair of the LLNL IRB.

For further information on records retention or preparing records for shipment to storage, contact the LLNL Records Manager.

2.9.5 Completion/Termination of Study

To formally complete a study file, the IRB requests that investigators officially notify the IRB Office when a study is terminated or completed or after data analysis is complete. As part of the close-out process, investigators are also asked to submit a 1-2 paragraph summary of the study's results.

3.0 The Institutional Review Board

3.1 Introduction

According to 45 CFR 46.113, the IRB has the authority to approve, to require modification of, and to disapprove proposed human subjects research. The IRB also has the authority to require progress reports from investigators, to oversee the conduct of a study, and to suspend or revoke its approval of ongoing research. Failure to comply with IRB requirements is considered serious misconduct and may be subject to sanctions including possible termination of approved research. The IRB is supported by the IRB Office. At LLNL, the IRB Chair and the IRB Office report directly to the Authorized Institutional Official.

3.2 Membership and Responsibilities of the IRB

To maintain a review process that is responsive to the concerns of all involved, federal regulations require that the IRB membership reflect experience, expertise, and diversity in academic, research, and professional background; racial and cultural heritage; and a sensitivity to community attitudes. The IRB is responsible for ensuring that all approved research complies with the letter and spirit of human subject protection regulations as well as the three principles previously defined in the Belmont Report: respect for persons, beneficence, and justice.

3.2.1 IRB Members

Consistent with federal regulations, the LLNL IRB is comprised of at least five members from diverse backgrounds who have the professional competence necessary to completely and adequately review human subjects research activities commonly conducted by LLNL. Consideration is also given to how the member's background will contribute to the diversity of the Board. To promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, prospective Board members must also be sensitive to such issues as community attitudes.

The LLNL IRB includes:

- both male and female members,
- at least one member whose primary expertise is in a non-scientific area, and
- at least one member who is not otherwise affiliated with the Laboratory, and who is not a part of the immediate family of a person affiliated with the Laboratory.

The names and qualifications of current IRB members are included in Appendix 12.

Members are appointed by the Authorized Institutional Official, at the recommendation of the IRB Chairman. Appointments are for three-year terms. Terms are renewable at the discretion of

the IRB Chair and with the concurrence of the member. New members attend their first meeting as observers only. Members do not receive financial compensation.

3.2.1.1 Attendance Expectations

IRB members are responsible for attending all scheduled IRB meetings, reviewing all assigned materials, and participating in IRB discussions. Members are asked to notify the IRB Office of their impending absence at least two weeks prior to the scheduled IRB meeting. More than two absences during a 12-month period may result in removal from the board.

3.2.1.2 Conflicts of Interest

In the event that an IRB member has a conflict of interest with any protocol submitted for review, that member must disclose this conflict to the IRB Chair prior to the Board's review of the protocol. They may respond to questions from Board members. However, they must remove themselves from the room prior to the Board's deliberation and vote on the protocol. The official minutes will reflect that the member removed him/herself from the IRB meeting during the final discussion and vote on the protocol.

3.2.1.3 Sub-Committee Membership

All members are asked to participate on at least one sub-committee. Current sub-committees include dosimetry, education, and process review. Requests for preferences will be honored, if possible.

3.2.1.3.1 Dosimetry and Toxicology Sub-committee

Protocols that involve the ingestion or injection of radiation or other toxic materials will be sent to the Dosimetry and Toxicology Sub-committee for review prior to the convened meeting. The Sub-committee provides the IRB with assurance that a proper review has been conducted by an independent, third-party with regards to exposure or dosimetry estimates to ensure that potential risks are identified for evaluation by the IRB. The Sub-committee will verify that:

- documentation is consistent with IRB written requirements,
- methods used are clearly described and appropriate for the agent,
- qualifications of the third-party reviewer are documented, and
- dosimetry and exposure estimates are clearly documented and technically valid.

3.2.1.3.2 Education Sub-committee

The Education Sub-committee provides guidance to the IRB Office and participates in identifying and developing educational and outreach activities for Board members and investigators. This includes education programs at IRB meetings and LLNL-wide educational activities.

3.2.1.3.3 Process Review Sub-committee

The Process Review Sub-committee provides guidance to the IRB Office on streamlining and clarifying IRB policies and procedures. This includes initial review of all proposed revisions or additions to new or existing policies and IRB forms.

3.2.1.4 Board Member Education Programs

All new IRB members receive an orientation from the IRB Office before starting their active service. This orientation includes an overview of the Federal regulations (45 CFR 46, 21 CFR 50 and 21 CFR 56) established to protect human research subjects, the Belmont Report, and other documents/materials pertaining to the protection of human research subjects at LLNL. Copies of these materials will be made available to new Board members at their orientation. New members will be mentored by a senior IRB member during their first year on the Board. Selection and teaming of new members with mentors will be by mutual agreement.

The IRB Office staff will provide continuing education and support to all IRB members. Members receive a copy of the Human Research Report, or similar journal, on a monthly basis. Human subjects research-related news articles will be provided to IRB members as deemed appropriate by the IRB Chair or IRB Office. Other pertinent reference materials relating to human subjects research issues are available for review in the IRB Office. The IRB Office will also, on occasion, sponsor educational lectures. All IRB members will be strongly encouraged to participate in scheduled educational events.

3.2.1.5 Participation in the Expedited Review Process

All board members are asked to participate in the expedited review process. Based on experience and background, the IRB Office will select one or two Board members to review protocols qualifying for expedited review. Protocols involving dosimetry issues will have a member of the dosimetry sub-committee assigned as one of the primary reviewers, or as a third member. IRB members will participate on a rotating schedule. During the review process each reviewer is asked to contact the investigator or the IRB Office, as needed, and write a final report with his/her decision to approve the protocol or to refer it to full board for review. Reviewers are asked to complete an initial review of the protocol within 5 working days and to communicate those results to the IRB Office.

3.2.1.6 Removal from the Board

Recommendations for removal, along with a written justification, must be presented by the IRB Chair to the Authorized Institutional Official for consideration and final decision (except in cases of absenteeism).

3.2.2 IRB Chairperson

The Chair is appointed by the Laboratory Director and serves at the Director's discretion. Only senior level staff may recommend that a Chair be removed from office. This recommendation, along with a written justification, must be presented to the Authorized Institutional Official and the Laboratory Director for consideration and final decision.

The Chair is a voting member on all IRB issues unless s/he has a conflict of interest with a protocol under IRB review. The duties of the IRB Chair include moderating meetings, performing expedited reviews, consulting with investigators as needed, coordinating other efforts with the IRB administrative staff as needed, and recommending new members to the Authorized Institutional Official for consideration and final appointment. Typically, the Chair does not sit on any of the IRB sub-committees.

3.3 IRB Meetings

Convened meetings of the IRB are usually held on the second Wednesday of every other month, starting in January. Dates and times of the meetings can be found on the IRB Web site at http://www.llnl.gov/HumanSubjects/, or by calling the IRB Office at (925) 422-8069. Ad hoc meetings may be called to address specific protocol issues. IRB Office staff typically contact Board members approximately two to three weeks before a meeting to confirm attendance and ensure that quorum is achieved.

Full-board discussions require a majority of Board members (51%) to be present during protocol discussions. One of the attendees must be a non-scientific member. A majority of members present (51%) must vote to approve or disapprove a protocol. Proxy votes are not permitted. In the event that an IRB member has a conflict of interest with any protocol submitted for review, that member must disclose this conflict with the IRB Chair. The member will not be allowed to participate in the study's deliberation/discussion, vote on the study's approval/disapproval, or be counted towards quorum requirements for that particular protocol.

Board members receive copies of protocol packets, including supporting documentation, and any other documents relating to items on the agenda approximately one week before the meeting.

3.4 IRB Review Process

The IRB is responsible for ascertaining the acceptability of proposed research in terms of institutional commitments and regulations, applicable laws, standards of professional conduct and practice, and ethical and societal norms. When the LLNL IRB reviews research involving a category of vulnerable subjects (e.g., prisoners, children, or individuals institutionalized as mentally disabled), the Board will include in its reviewing body one or more individual(s) who have as primary concern the welfare of these subjects. If no members of the Board have the appropriate background, the Board will use consultants on an as-needed basis during the review

process. Consultants are not allowed to vote on the approval or disapproval of the protocol under review.

The IRB examines subject recruitment procedures, proposed remuneration (in cash or in kind), and the informed consent process. The Board also evaluates the potential risks and benefits to participants outlined in each protocol. This review helps to ensure that investigators recruit subjects in an equitable, non-coercive manner, that subjects are fully informed about the risks and benefits entailed in participation, and that subjects are not exposed to disproportionate risks.

3.4.1 Levels of IRB Reviews

The review of applications to involve human subjects in research is a multi-step process. The process begins with the submission of an application to the IRB Office who screens the initial application packet and corresponds with the investigator if clarification is needed on any part of the application. Once the screening has been completed, the protocol is submitted to the Board for review.

New and continuing protocols may undergo one of two levels of Board review, full board or expedited review. In some cases, the IRB Office, in consultation with the IRB Chairman, may determine that a protocol requires only administrative review by the IRB Office, in which case the investigator will be contacted within three (3) working days. Amendments or modifications to currently approved protocols must also be reviewed by the IRB.

During the review process, the Board examines the protocol and supporting documentation to ensure that the investigator has addressed the risks and benefits posed to potential subjects participating in the research, the subject selection is equitable, and that the consent process will provide adequate information to prospective subjects so that subjects can make informed decisions regarding their participation in the research activity. Any issues or concerns identified during the IRB review will be communicated to the investigator within three to five (3–5) business days following completion of the review. This communication most often takes the form of an email correspondence from the IRB Office. Receiving correspondence from the IRB Office after a review by the IRB is typical and should not be viewed as a negative comment about the content of the research.

The Board review process allows investigators various levels of appeal from the time a study receives initial review through approval or disapproval. Any and all IRB decisions are contingent upon the response of the investigator. If the Board finds that the negotiation is at an impasse, the Board may request an intramural and/or extramural independent consultant review.

Research that has been approved by the IRB may be subject to further appropriate review and approval or disapproval by LLNL management. However, management may not approve research if it has not been approved by the IRB.

Investigators should be aware that the review process can take up to two months. Because some sponsors require IRB approval prior to consideration of proposals for funding, and all require IRB review prior to release of funding for human subjects research activities, investigators are

strongly advised to contact the IRB Office regarding IRB submission deadlines and the current IRB meeting schedule.

A discussion of the various types of review follows.

3.4.1.1 Research Requiring Review by the Convened Board (Full-Board Review)

Except for research qualifying for an expedited review, all protocols must be reviewed during convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it must receive approval from a majority of those members present at the meeting.

When submitting a study for full-board review, investigators should allow three (3) weeks lead time for the processing of the human subjects application by the IRB Office staff prior to the IRB meeting. The IRB Office staff logs each submission and check to ensure it fulfills all application requirements. The staff will inform investigators by telephone, email, or letter if the application is missing elements. All complete applications are copied and distributed to all members of the Board. A thorough and intelligent analysis of the application requires that each Board member receive a complete set of materials to review prior to the meeting. The members receive materials approximately one (1) week prior to the scheduled meeting.

Reviews by the convened Board can take up to two (2) months from the date of submission until the Board identifies necessary clarifications and modifications. In the event that no additional information or modification is required, the IRB may approve a study within this time period. Investigators should be aware that initial Board review most often results in a request for additional information, clarification, or revisions to the protocol prior to the Board giving final approval of the research protocol.

Consideration, discussion, and a vote regarding the proposed research must occur during a properly convened meeting of the IRB. During the meeting, the investigator will be asked to briefly describe his/her research protocol and answer any questions that Board members may have. Following the Q&A period, the investigator is asked to leave and the Board continues their deliberations. These deliberations will include a detailed examination of the protocol, the Consent Form, and all supporting documentation, including any questionnaires or survey instruments and any recruiting materials.

The Board may come to one of four (4) determinations regarding a request to involve human subjects in research:

1. **Approved as submitted**—An approval letter is sent to the investigator within three to five (3–5) working days. A copy of the approval letter is also sent to the investigator's supervisor.
2. **Approved pending completion of minor modifications and/or clarifications**—The Board will direct the IRB Staff to correspond with investigators regarding clarification of minor points and/or modifications to the protocol or Consent Form. An investigator's response to IRB correspondence may be approved by the Chairman, a designated Board member, or sub-committee without review by the full Board. The Chairman, designated

member, or sub-committee may not disapprove a response, but they may request additional information from the investigator or refer the response to the full Board for additional review.

3. **Deferred**—Studies are deferred when the IRB has substantive concerns or significant requests for clarification. Responses to IRB correspondence in this category will be resubmitted to the full Board for further deliberation.
4. **Disapproved**—Investigators have the right to directly discuss with the Board requests for revision and decisions of disapproval. The IRB, however, retains the final authority for approval of proposed research with human subjects.

Results of Board decisions are reflected in correspondence sent to investigators within approximately three to five (3–5) working days following the IRB meeting. Letters or emails sent to investigators will describe any conditions required for approval, may request additional information, and will indicate the next step, if any, in the review process.

During the review process, the Board will also determine whether the protocol requires review more often than on an annual basis.

3.4.1.2 Research Eligible for Expedited Review

Expedited review, as defined by 45 CFR 46.110, allows the IRB Chairman, an individual Board member, or a designated sub-committee of the IRB, to evaluate and approve specific types of minimal risk research. All studies received by the IRB Office are evaluated for possible expedited review. If the Office determines that a protocol qualifies for expedited review, and the IRB Chairperson concurs, the complete protocol packet is given to one or more Board members for review. Reviewers conducting an expedited review may exercise all of the authority of a convened Board meeting except that they may not disapprove a study. When the reviewer(s) cannot approve the research under expedited review, the study will be referred to the full Board for review at the next scheduled meeting. Investigators should note that some of the expedited review categories may not apply to "vulnerable" populations, such as pregnant women, in vitro fertilization, children, prisoners, or mentally incompetent persons.

Investigators will receive written notification of IRB action resulting from an expedited review. Such action may include approval or a request for further information. Information about research protocols approved under expedited review will be provided to Board members during a legally convened meeting of the full Board.

> ***Note**: Minimal risk is the probability and magnitude of harm or discomfort anticipated in the research are not greater, in and of themselves, than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

According to 45 CFR 46, research involving no more than minimal risk may receive expedited review. Additionally, the involvement of human subjects must fall into one or more of the following categories:

- The study of existing data documents, records, pathological specimens, or diagnostic specimens.
- Collection of blood samples by venipuncture, in amounts not exceeding 550 milliliters in an eight-week period, and not more than two times per week from subjects 18 years of age or older who are in good health and not pregnant, and weigh at least 110 lb.
- Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.
- Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
- Collection of hair and nail clippings in a non-disfiguring manner or deciduous teeth and permanent teeth, if patient care indicates a need for extraction.
- Collection of mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings, or sputum collected after saline mist nebulization.
- Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of teeth and the process is accomplished in accordance with accepted prophylactic techniques.
- Recording of data from subjects 18 years of age or older using non invasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic exhography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (e.g., x-rays, microwaves).
- Moderate exercise by healthy volunteers.
- Voice recordings made for research purposes, such as research of speech defects.
- Research on individual or group characteristics or behavior, or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
- Review of minor changes in previously approved research or for cases where all protocol-related interventions have been completed and the protocol remains active only for long-term follow-up on subjects.

> ***Note**: The activities listed above should not be considered minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.*

The expedited review procedure may **not** be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections have been implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may **not** be used for classified research involving human subjects.

> ***Note**: Standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.*

3.4.1.3 Review of Classified or Sensitive Human Subjects Research

Classified or sensitive projects require review by the convened IRB. Normal review in an unsecured environment is preferred as long as the research can be accurately and comprehensively described to the IRB, and no classified or sensitive information is relevant to the protection of human subjects. If the research cannot be subjected to normal review, the Chair of the IRB may determine that it should be reviewed at a meeting of the IRB conducted in a secure environment. A majority of the members of the IRB, including at least one nonscientist, must be present at this meeting. Each member present must have the appropriate security clearance.

3.4.1.4 Amendments and Modifications to Currently Approved Research

Substantive changes in research during the period for which IRB approval has already been given shall not be initiated by investigators without IRB review and approval. The only exception to this policy is if it becomes necessary to revise a protocol to eliminate apparent immediate hazards to the subject. These changes must be reported immediately to the IRB.

Amendments or modifications to previously approved research, submitted between scheduled continuing reviews, that involve only minor changes in previously approved protocols or minor changes in Consent Forms may qualify for expedited review. Only changes that do not increase

the risk to research subjects may receive an expedited review. Modifications to approved protocols that may affect the risk to subjects are forwarded to the full Committee for review. (See Section 2.9.2 for further information about modifying currently approved research.)

3.4.1.5 Continuing Reviews

All protocols that have been approved by the IRB will be reviewed on a continuing basis at intervals appropriate to the degree of risk as determined by the IRB, but not less than once per year. The IRB will determine the frequency of continuing review when it grants final approval to a proposed study. A standard approval letter will be used to notify the investigator of the approval and length of approval for each proposal. The IRB may be called into an interim review session by the Chairperson at the request of an IRB member or investigator to consider any matter concerned with the rights and welfare of any subject.

3.4.1.6 Additional Types of Review

The IRB will determine whether a project requires more than annual review and may require an appropriate monitoring procedure that could include monitoring of the consent process, observation of the research procedures, verification from a third party that there have been no material changes in the research since the previous review, and review of research-related records.

3.4.2 Review Criteria

3.4.2.1 Protocols

In light of the information provided in the research plan of the protocols, the IRB determines whether protection of human research subjects is adequate, in accordance with the following criteria.

3.4.2.1.1 Risks

The IRB will identify the risks associated with the research and will determine whether risks, if any, to a subject are reasonable in relation to the anticipated benefits and the importance of the knowledge that may reasonably be expected as a result. The IRB must also determine if risks to subjects are minimized by (1) using procedures that are consistent with sound research design and do not unnecessarily expose subjects to risk and (2) using procedures that are already being performed on the subjects for diagnostic or treatment purposes, whenever appropriate.

Where appropriate, the IRB will determine whether the research plan makes adequate provision for monitoring the data collected to assure the safety of the subject, and that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The IRB is also required to ensure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits and to determine intervals of periodic review.

The IRB will not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3.4.2.1.2 Subject selection

The IRB will determine that the selection of subjects is equitable. In making this assessment, the IRB shall take into account the purposes of the research, the setting in which the research will be conducted, and the population from which subjects will be recruited.

Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons who are economically disadvantaged, or employees for whom the research investigator has supervisory responsibility, the IRB will determine that appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

3.4.2.1.3 Incentives for participation

The IRB will review any proposed reimbursement (in cash or in kind) that the subject will receive as a result of participating in the research activity. Although the practice of paying subjects to participate in research has long been an integral part of the recruitment process, the Board must determine that payments do not represent "undue inducement" by leading to a decrease in either the voluntariness or the understanding with which subjects agree to participate. The Board must also determine that payments to subjects do not result in economically disadvantaged populations bearing an unduly large share of the risks and burdens of research participation.

3.4.2.2 The Informed Consent Process

The IRB will carefully evaluate the informed consent process: when, where, and how consent is obtained and any provisions for the ongoing consent of subjects. Federal regulations on informed consent stipulate eight (8) basic required elements of consent, and note six (6) additional elements that may be added to a consent form when appropriate. The IRB will verify that these elements have been incorporated into the consent document. The consent document must present all necessary information to the prospective subject in as clear and easily readable a manner as possible. Please see Section 2.8, "The Consent Process", for additional information and guidance regarding the informed consent process and developing a Consent Form.

The IRB will determine that informed consent (1) is obtained from the subject or the subject's legally authorized representative, (2) is written in language understandable to the subject or the representative, (3) is obtained under circumstances that offer the subject or the representative sufficient opportunity to consider whether the subject should or should not participate, and (4) does not include exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights or releases or appears to relieve the research investigator, the sponsor, or the institution or its agents from liability for negligence.

The IRB will also determine that informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117. If the research activity is subject

to FDA regulations, informed consent will be obtained in accordance with 21 CFR 50.23 and 21 CFR 50.24. (See Section 2.8.1.2 for details about waivers of informed consent.)

3.4.2.2.1 Basic elements of consent

The IRB will determine that informed consent will be obtained in a manner and method that meets the requirements of 45 CFR 46.116. Specifically, the IRB will determine that subjects have been informed of the following:

- that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
- a description of any reasonably foreseeable risks or discomforts to the subject;
- a description of any benefits to the subject or to others that may reasonably be expected from the research;
- a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- the extent, if any, to which confidentiality or records identifying the subject will be maintained;
- for research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of and where further information may be obtained;
- who to contact for answers to pertinent questions about the research and research subjects' rights, and who to contact in the event of a research-related injury to the subject;
- that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

3.4.2.2.2 Additional elements of informed consent

Per 45 CFR 46.116(b), several additional pieces of information are required when, in the judgment of the IRB, they are appropriate. These additional elements are as follows:

- a statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
- any anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- any additional costs to the subject, or their insurance carrier, that may result from participation in the research;
- the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

- a statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and
- the approximate number of subjects involved in the study.

3.4.2.2.3 FDA requirements for informed consent

For research involving FDA-regulated products, a statement that the FDA is authorized to inspect all records associated with the research must be included on the Consent Form.

3.4.2.3 Qualifications of Research Personnel

Procedures requiring special skills on the part of the investigators, licensure, accreditation, and/or experience in qualifying the investigator for the performance of the proposed procedures are reviewed by the IRB. In addition, the IRB will consider the facilities and equipment used to conduct the research and maintain the rights and welfare of the subjects.

3.4.3 Termination of IRB Approval

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, appropriate institutional officials, OHRP, any other sponsoring federal agencies, and/or private sponsors, if appropriate.

4.0 The Institutional Review Board Office

4.1 Introduction

The IRB Office is responsible for providing a full range of administrative support on matters related to IRB reviews of human subjects research, including assuring LLNL's adherence to federal regulations governing human subjects. Resources for the IRB Office are made available through funding from the Deputy Director for Science and Technology. The Office works closely with Board members to develop broad-based educational activities for Board members, investigators, and the LLNL community to raise the level of awareness regarding human subjects research issues. The Office interacts with multiple levels of personnel across LLNL directorates, at DOE and other federal agencies, at University of California campuses and the UCOP, and at other IRB sites to coordinate activities and to gather, clarify, and disseminate information relevant to human subjects research at LLNL. The Office is also available to assist investigators with questions or concerns they may have regarding the development or conduct of human subjects research protocols

The IRB Office reports to the Authorized Institutional Official.

4.2 Initial Review Determinations

The determination that an activity involving human subjects is exempt from federal regulations is made by the IRB Office. To make this determination, the IRB Office will ask the following questions:

- **Is the activity research?** Occasionally, an investigator is unsure whether or not an activity involving human subjects would be considered research. In those cases, investigators are encouraged to contact the IRB Office for an administrative review. The IRB Office will review supporting documentation of the activity and notify the investigator if additional IRB review is required.

  45 CFR 46 defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities."

- **Does the activity involve human subjects or their bodily materials?** The IRB Office will review the involvement of human subjects in the research activity to ensure that they are "living individuals about whom the investigator obtains (1) data through intervention or interaction with the individual or (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects."

- **Is the research activity exempt from 45 CFR 46?** Some research involving human subjects or their bodily materials does not require review and approval by the IRB (see Section 2.3). If an investigator believes his/her human subjects research activity falls into any of the listed categories, s/he must submit Form HSR-4, "Request for Administrative Review".

> ***Note**: Investigators cannot "self-exempt" from IRB review. LLNL has assured DHHS that the evaluation and certification of exempt status is performed by the IRB Office, which reviews all such activities, whether funded or not, and certifies that the research meets the federal requirements for an "Exempt Determination".*

4.2.1 Submitting a Protocol for Administrative/Exempt Review

When submitting a research activity to the IRB Office for an administrative review, the investigator must provide the following documents, as applicable:

- A "Request for Administrative Review" (Form HSR-4)
- A brief abstract of the research activity, purpose, and objectives of the study.
- Approval from other participating institutions.
- Recruitment materials, i.e., advertisements, flyers, phone scripts, etc.
- A sample consent form or information sheet.
- Copies of surveys, educational tests, or interview scripts.

Investigators are strongly urged to consult with the IRB Office before submitting a "Request for Administrative Review".

4.2.2 Submitting a Request for Fee-for-Service Determination

When submitting Form HSR-7, "Request for Fee-for-Service Determination," the IRB Office will require the LLNL investigator to provide a letter from the Chair of the reviewing IRB containing the following information:

- Title of study
- Date of IRB approval
- Information regarding vulnerable populations (i.e., pregnant women, fetuses, children, prisoners, or the decisionally impaired). Specifically, will the study involve vulnerable populations? If yes, the vulnerable population should be identified.
- Acknowledgement that samples will be analyzed at LLNL as a fee-for-service activity.
- The reviewing IRB's Multiple Project or Federal-wide assurance number.

4.3 Documentation of IRB Activities

The IRB Office is responsible for preparing and maintaining adequate documentation of IRB activities, including the following:

- Copies of all research proposals reviewed; scientific evaluations, if any, that accompany the proposals; approved sample consent documents; recruiting materials; and progress reports submitted by investigators.
- Reports and results of subsequent reviews by the IRB of injuries to subjects and/or other adverse events.
- Records of continuing review activities including the timeliness of progress reports, and the IRB decision to append, terminate, or to allow study continuance as previously approved.
- Copies of all correspondence between the IRB and the investigators.
- Notification to the full committee, by inclusion on the IRB agenda, of protocols that have been approved via the expedited review process. The IRB Office will also notify Board members, by inclusion on the IRB agenda, of protocols that were submitted for administrative review.
- Agendas and minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the fact that an LLNL IRB member with a conflicting interest in a study refrained from voting; the basis for requiring changes in or disapproving research; a written summary of the discussion of controverted issues and their resolution; and any other matters that may come before the Board during the meeting.
- A list of IRB members identified by name; earned degree; representative capacity; indication of experience such as board certifications, licensures, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution.

4.4 IRB Office Reporting Requirements

The IRB Office promptly reports the following information to the IRB and the Authorized Institutional Official, the Office for Human Research Protections, the Program Manager for Human Subjects Research at the DOE, and (for studies involving FDA-regulated products) the FDA and sponsor:

- Injuries to human subjects.
- Unanticipated problems or scientific misconduct involving risks to human research subjects or others.
- Serious or continuing noncompliance by investigators with the requirements of the Federal regulations.
- Suspension or termination of IRB approval as a result of adverse events or serious and continuing noncompliance by investigators.
- Changes in IRB membership.

Additionally, the DOE Program Manager for Human Subjects Research requires that the IRB Office submit quarterly reports on LLNL IRB activities in addition to annual submissions of abstracts for all human subjects research protocols that have been reviewed by the LLNL IRB.

Appendices